
# Cobalt-Catalysed Alkylative Aldol Cyclisations Using Trialkylaluminium Reagents

# Rhodium-Catalysed Carbometallation of Ynamides in the Preparation of Multisubstituted Enamides

Thesis Submitted in Accordance with the Requirement of The University of Edinburgh for the Degree of Doctor of Philosophy
By

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**MChem (Hons) with a Year in Industry**

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# Declaration

I hereby declare that, except where specific reference is made to other sources, the work contained within this thesis is the original work of my own research since the registration of the PhD degree in September 2006, and any collaboration is clearly indicated. This thesis has been composed by myself and has not been submitted, in whole or part, for any other degree, diploma or other qualification.

Signed

Mairi Ellen Rudkin

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# List of Abbreviations

| | |
|---|---|
| Ac | acetyl |
| acac | acetylacetonate |
| aq | aqueous |
| Ar | aryl |
| BBN | 9-borabicyclo[3.3.1]nonane |
| Bn | benzyl |
| Boc | *t*-butyloxycarbonyl |
| br | broad |
| Bz | benzoyl |
| cat. | catalyst |
| cod | 1,5-cyclooctadiene |
| Cp | cyclopentadienyl |
| Cy | cyclohexyl |
| d | doublet |
| dba | dibenzylideneacetone |
| DBU | diaza(1,3)bicyclo[5.4.0]undecane |
| DIBAL-H | diisobutylaluminium hydride |
| DMA | dimethylacetamide |
| DMAP | 4-(dimethylamino)pyridine |
| DME | dimethoxyethane |
| DMF | *N*,*N*-dimethylformamide |
| DMI | 1,3-dimethyl-2-imidazolidinone |
| DMSO | dimethylsulfoxide |

| | |
|---|---|
| dppe | 1,2-bis(diphenylphosphino)ethane |
| dppf | 1,1'-bis(diphenylphosphino)ferrocene |
| dppb | 1,4-bis(diphenylphosphino)butane |
| dr | diastereomeric ratio |
| ee | enantiomeric excess |
| EI | electron impact |
| equiv | equivalent |
| ES | electrospray |
| EWG | electron-withdrawing group |
| fod | 6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionate |
| FT | Fourier transform |
| g | gram |
| h | hour |
| HMPA | hexamethylphosphoramide |
| HRMS | high resolution mass spectrometry |
| IR | infrared spectroscopy |
| LDA | lithium diisopropylamide |
| MEM | $\beta$-methoxyethoxymethyl |
| m | multiplet |
| mg | milligram |
| min | minute |
| mL | millilitre |
| Ms | mesyl |
| MS | molecular sieves |
| NHC | *N*-heterocyclic carbene |
| NMDPP | (+)-(neomenthyl)diphenylphosphine |

| | |
|---|---|
| NMO | *N*-methylmorpholine |
| NMP | *N*-methylpyrrolidone |
| NMR | nuclear magnetic resonance spectroscopy |
| OMP | 2-methyloxyphenyl |
| PCC | pyridinium chlorochromate |
| pin | pinacol |
| PMP | 4-methoxyphenyl |
| ppm | parts per million |
| q | quartet |
| rr | regioisomeric ratio |
| rt | room temperature |
| s | singlet |
| t | triplet |
| TBAF | tetrabutylammonium fluoride |
| TBME | *t*-butyl methyl ether |
| TBS | *t*-butyldimethylsilyl |
| TC | thiophene-2-carboxylate |
| Tf | trifluoromethanesulfonate |
| THF | tetrahydrofuran |
| TLC | thin layer chromatography |
| TMDS | tetramethyldisiloxane |
| TMEDA | tetramethylethylenediamine |
| TMS | trimethylsilyl |
| Ts | tosyl |
| UV | ultraviolet spectroscopy |

# Abstract


## I. Cobalt-Catalysed Alkylative Aldol Cyclisations Using Trialkylaluminium Reagents

The cobalt-catalysed alkylative aldol cyclisations of α,β-unsaturated amides with an appendant ketone were studied using a range of trialkylaluminium reagents. Investigations revealed that $Co(acac)_2 \cdot 2H_2O$ acts as an effective precatalyst for this transformation and the reaction provides β-hydroxylactam products containing three contiguous stereocentres with high levels of diastereoselection. The substrate scope of the reaction was explored and attempts were made to develop an asymmetric variant of this process. Two plausible reaction mechanisms have been proposed; the first invokes a π-allylcobalt species as a key intermediate in the reaction mechanism and the second involves a radical-mediated pathway. A stereochemical rationale for the observed relative stereochemistry of the β-hydroxylactam products has been discussed.

## II. Rhodium-Catalysed Carbometallations of Ynamides in the Preparation of Multisubstituted Enamides

A highly stereo- and regioselective rhodium-catalysed carbozincation of ynamides using organozinc reagents has been disclosed. A careful examination of ligand effects on the rhodium catalyst yielded a complementary set of hydrozincation conditions. The alkenylzinc intermediates produced during the course of these reactions have been harnessed in further transformations with electrophilic species and in cross-couplings, thus providing access to multisubstituted enamides in a stereo- and regioselective fashion. Additionally, a rhodium-catalysed tandem carbometallation–conjugate addition with *ortho*-boronate substituted cinnamic acid derivatives has been described. The enamide–indene products were obtained in good yields and regioselectivities. Preliminary work has been undertaken on an asymmetric variant of this transformation and the initial results have been reported.

# Contents

# 1.0 Conjugate Addition of Trialkylaluminium Reagents to α,β-Unsaturated Carbonyl Compounds and Tandem Conjugate Addition–Aldol Reactions

Transition metal-catalysed domino reactions initiated by conjugate additions are a powerful set of transformations in organic synthesis; these reactions potentially allow rapid increases in complexity in a single step with high levels of stereocontrol.[1] The alkylative aldol cyclisation, which involves the conjugate addition of an organometallic reagent to an α,β-unsaturated carbonyl compound and subsequent trapping of the resultant metallaoenolate with an aldehyde or ketone, is an important subset of these. Most protocols utilise enones as the Michael acceptor, alongside dialkylzinc or organoborons as the carbon-based nucleophile. Expansion to other types of α,β-unsaturated acceptor and nucleophiles would result in a wider variety of products which is highly desirable. In the following chapter we report a cobalt-catalysed alkylative aldol cyclisation using trialkylaluminium reagents. Accordingly, we will first examine transition metal-catalysed conjugate additions of trialkylaluminium reagents to α,β-unsaturated acceptor substrates and then review the alkylative aldol reaction, to appreciate how the current work complements the existing literature.

## 1.1 Conjugate Addition of Trialkylaluminium Species to α,β-Unsaturated Carbonyl Compounds

The carbon–carbon bond-forming reaction is arguably one of the most important synthetic transformations in organic chemistry. The metal-catalysed introduction of an alkyl or aromatic group onto an α,β-unsaturated system *via* conjugate addition is an effective way of achieving this goal. Classically, Grignard and organolithium reagents were employed to effect this reaction. However, a high level of reactivity renders them unsuitable for substrate classes that are more highly functionalised. Consequently there has been a significant volume of literature on transition metal-catalysed conjugate additions of *less reactive* organometallic reagents and their asymmetric variants. In particular, the copper-catalysed conjugate addition of

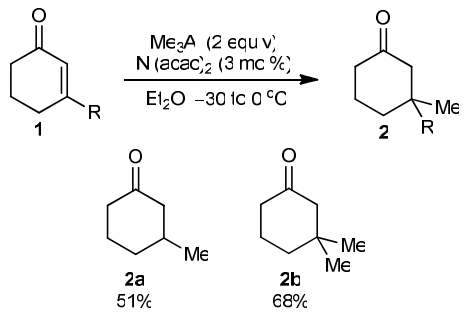
dialkylzinc reagents[2,3] and the complementary rhodium-catalysed conjugate addition of aromatic boronic acids[4,5] to α,β-unsaturated carbonyl compounds have been extensively studied.

Surprisingly, the metal-catalysed conjugate additions of trialkylaluminium reagents have been less well documented, despite a ready availability of trialkylaluminium reagents commercially and facile preparation of more exotic variants.[6] The greater Lewis acidity of these reagents in comparison with dialkylzinc reagents, offers a wealth of potential in developing catalytic conjugate addition reactions to a wider variety of more challenging substrates.

### 1.1.1 Non-Enantioselective Conjugate Addition

The focus of this review is on the *metal-catalysed* conjugate addition of trialkylaluminium reagents to α,β-unsaturated carbonyl compounds; however, a large proportion of the early literature in this area concerned the *uncatalysed* reaction. This topic will not be discussed here but a recent review by von Zezschwitz[6] gives an extensive overview of the subject.

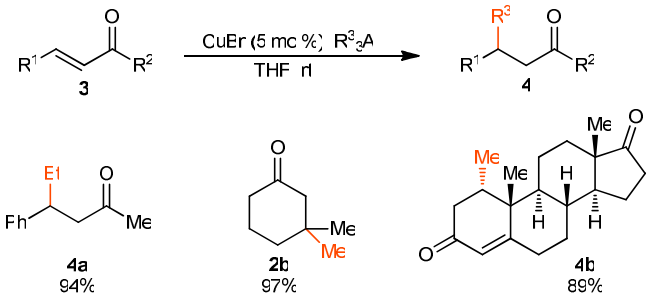
Mole and co-workers made the first report of a metal-catalysed conjugate addition of trialkylaluminium reagents to enones[7] and it was quickly followed by a study of the same reaction by Ashby and Heinsohn.[8] Both groups observed that a combination of $Ni(acac)_2$ and trimethylaluminium ($Me_3Al$) gave exclusively the 1,4-addition products of the enone substrates investigated (Scheme 1.1).




**Scheme 1.1**

The only side-products observed were oligomeric products arising from the Michael reaction of the intermediate aluminium enolates onto the starting enone. It naturally followed that yields increased with steric hindrance around the β-carbon, as these provided more sterically hindered aluminium enolates that would not form oligomers as easily. In spite of the success of this catalytic system with cyclohexenone substrates, attempts to extend the methodology to cyclopentenones failed as the respective aluminium enolates polymerised rapidly. Mole's group reported that alternative acetylacetonate salts were also suitable as potential catalysts (including copper (II), cobalt (III), iron (II) and iron (III) salts) although the observed yields were lower. However, Heinsohn and co-workers only obtained unreacted starting material in the presence of the cobalt catalyst.

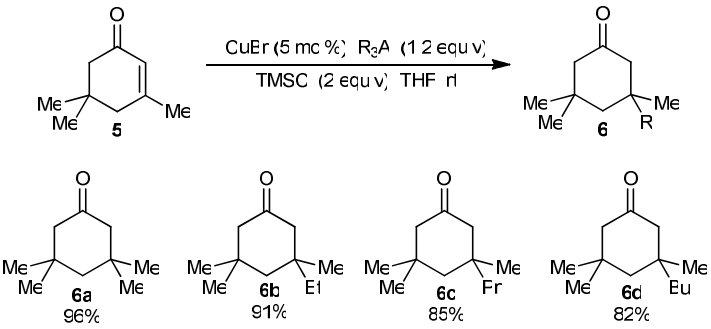
In 1993, Westermann and Nickisch drew inspiration from Mole's early work when they were attempting to effect a conjugate addition of a methyl group onto the steroidal enone to give **4b** (Scheme 1.2). They had previously observed that copper-catalysed additions of organolithiums and Grignard reagents to these steroids predominantly resulted in the 1,2-addition product. Fortuitously, the use of $Me_3Al$ in conjunction with a copper bromide catalyst cleanly gave the desired 1,4-addition product.[9] Earlier studies by the group had found that nickel catalysts were not as selective and resulted in significant amounts of the 1,2-addition product.




**Scheme 1.2**

Expansion of this methodology was successful and the conjugate addition products of a variety of acyclic, cyclic and steroidal enones were obtained in moderate to high

yields after reaction with either trimethyl- or triethylaluminium ($Me_3Al$ or $Et_3Al$). Later studies revealed that the conjugate addition reaction of higher organoaluminiums was promoted by the same catalytic system (Scheme 1.3).[10]



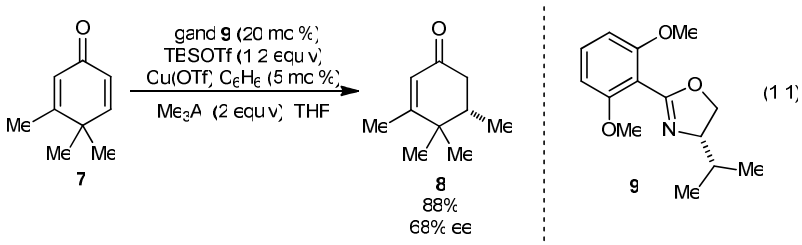

**Scheme 1.3**

Yields remained high for cyclic enones but were far lower for the acyclic examples. The presence of a TMSCl additive was found to increase the rate of reaction and it allowed significantly lower loadings of copper catalyst (0.1 mol%).[11]

### 1.1.2 Enantioselective Conjugate Addition

At this stage, the use of trialkylaluminium reagents was emerging as a potential solution to the problematic issue of conjugate additions to more challenging α,β-unsaturated acceptors. However, there was a growing need for enantioselective variants of this transformation in order for it to become a truly viable alternative to the more commonly used organometallic reagents.

The first example of an enantioselective metal-catalysed conjugate addition of a trialkylaluminium reagent to an α,β-unsaturated carbonyl compound was reported by Iwata and co-workers.[12] The group developed a system based on a copper triflate catalyst and a chiral 2-aryloxazoline ligand **9** (eq 1.1).




Conjugate addition to cyclohexa-2,5-dienone **7** had previously been poor-yielding with other organometallic reagents due to their lower reactivity and had additionally given low enantioselectivities. This methodology, which utilised the more reactive $Me_3Al$, provided the desired conjugate addition product in a good yield and a modest 68% ee. The presence of the TBSOTf additive was essential to raise the enantioselectivity to this level. In addition to providing a silyl activation of the dienone **7**, it was hypothesised that an interaction of the triflate anion with the copper complex resulted in a more rigid transition state (Fig 1.1).

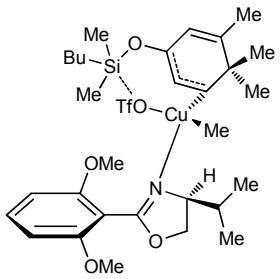
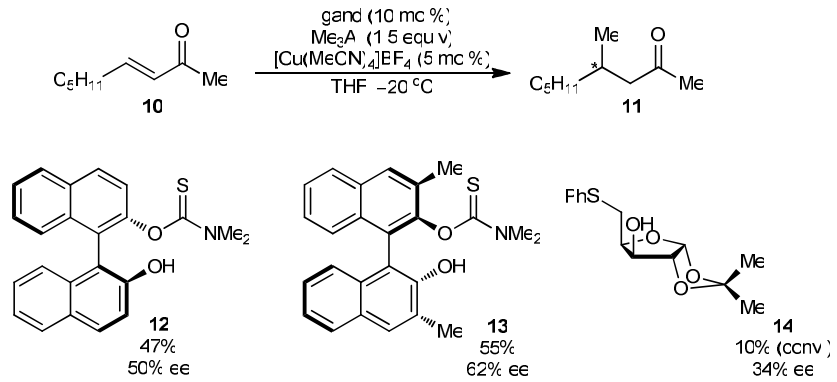


**Figure 1.1**

Woodward's group next published in this area, reporting a series of papers on three different sulfur-based ligands (Scheme 1.4).[13,14,15] All three classes of ligand were screened with the model system **10** and in all three cases the substrate scope was restricted to acyclic enones.



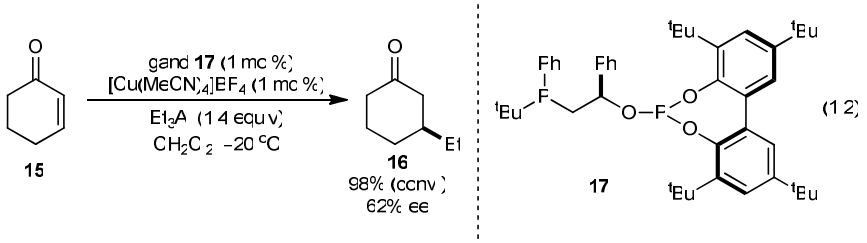

**Scheme 1.4**

The chiral thiourethane ligand **12** generally resulted in low enantioselectivities (the highest obtained was 50%) but it was notably the first report of a chiral thiourethane in an asymmetric catalytic process.[13] When $Me_3Al$ was replaced with the more reactive $Et_3Al$, it had a deleterious effect on both the yield and enantioselectivity of the reaction. The modified thiourethane ligand **13** resulted in a slight improvement to these results but the enantioselectivities still remained moderate.[14] Further studies revealed that both the 2-naphtholic directing group and the soft sulfur ligation site featured in **12** and **13** were critical in achieving the observed yields and levels of enantioselectivity.

A concurrent publication by the same group detailed a set of chiral dithioether ligands with a xylofuranose backbone (see ligand **14**, Scheme 1.4).[15] These ligands were easily prepared from xylose and gave high yields and reasonable levels of asymmetric induction for the 1,4-addition of $Et_2Zn$ to cyclohexenone. Unfortunately the corresponding conjugate addition of $Me_3Al$ to the model substrate **10** was limited to a maximum ee of 34%.

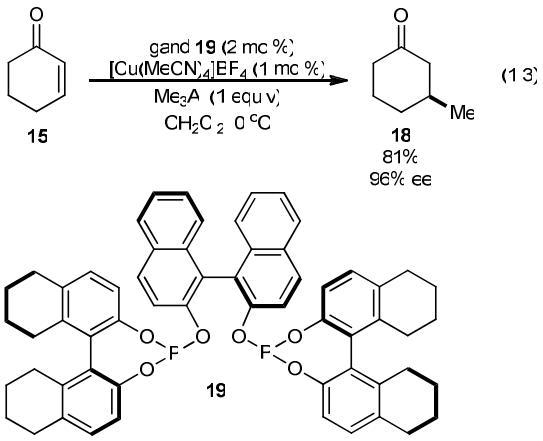
In 2000, van Leeuwen *et al* successfully developed the synthesis of a new class of phosphine–phosphite ligands and applied them to a number of asymmetric transformations. It had been shown previously that the contrasting nature of the two donor atoms in these ligands, namely an electron-donating phosphine and an electron-withdrawing phosphite, was able to affect the reactivity and selectivity of a

catalyst. These ligands were used advantageously in conjunction with a copper catalyst in the conjugate addition of $Et_3Al$ to cyclohexenone (eq 1.2).[16]

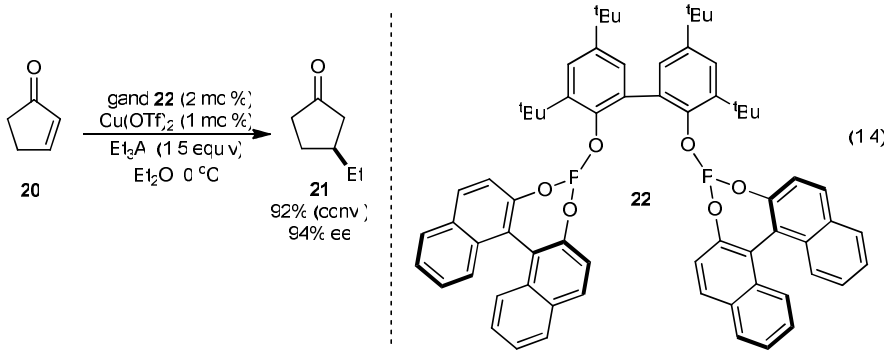



A small library of the phosphine–phosphite ligands was studied in this model system with both $Et_3Al$ and $Et_2Zn$; the structural variations that were investigated included different substituents at both the phosphorus atom of the phosphine moiety and at the stereogenic carbon adjacent to the phosphite and, additionally, the chain length of the linker. However, the group did not investigate any other type of phosphite moiety other than that featured in **17**. The best result obtained was a relatively moderate 62% ee with the phosphine–phosphite ligand **17**. Increasing the linker by one carbon resulted in a dramatic fall in enantioselectivity, as did the diastereomeric variations of **17**. The paper concluded that the configuration of the phosphine, the stereogenic centre next to the phosphite, the catalytic precursor and nature of the alkylating agent were significant in determining the enantioselectivity.

Subsequent investigations in this area by Chan and his group resulted in a new family of chiral aryl diphosphite ligands for the conjugate addition of $Me_3Al$ to cyclohexenone (eq 1.3).[17]



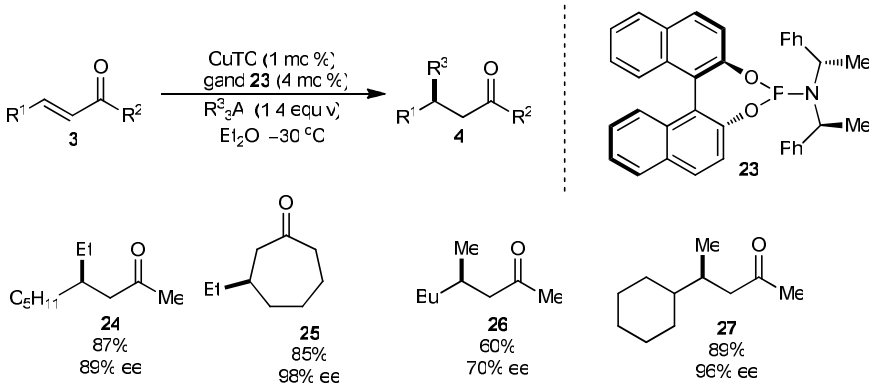
In this paper, exceptionally high levels of enantioselectivity were obtained for the model substrate cyclohexenone **15**. This result was a major improvement on the enantioselectivities previously obtained for the asymmetric conjugate addition reaction of trialkylaluminium reagents. Screenings of these types of ligand revealed that the asymmetric induction was dominated by the end groups of the chiral ligands. The same standard of results was achieved in the conjugate addition of $Et_3Al$ to 2-cyclopentenone (eq 1.4).[18]




Unfortunately, despite these highly promising results, the substrate scope of these reactions was never explored and the biaryl phosphite ligands have relatively complex structures that require an involved synthesis. However, the high enantioselectivities observed for these catalytic systems established that trialkylaluminiums could be a truly viable alternative to the more commonly used dialkylzinc reagents in asymmetric conjugate addition reactions.

To gain acceptance from the synthetic community and attain widespread popularity it is important that the transformation in question is technically simple and preferably uses commercially available materials. At this juncture, the conjugate addition of trialkylaluminium reagents had reached a high level of selectivity with a relatively simple procedure; unfortunately the highly specialised ligands, essential to achieving the high selectivity, were a major drawback. Therefore it was critical to create a catalytic system based on less complex ligands. In 2005, Alexakis and Woodward realised this ambition when they published their research into the asymmetric

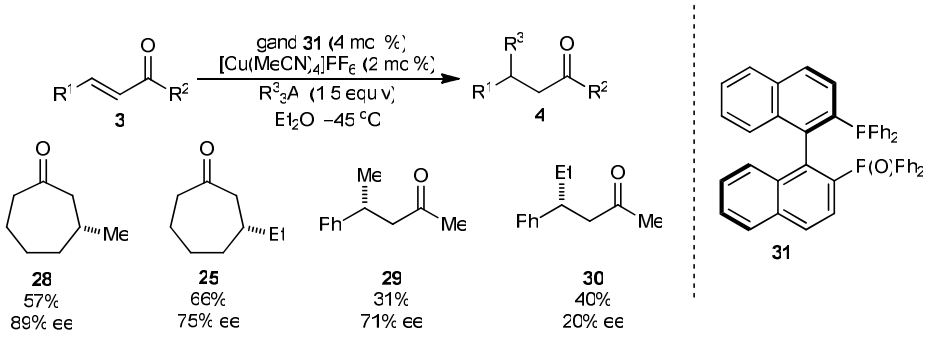
conjugate additions of organoaluminium reagents to enones using simple monodentate phosphoramidite ligands (Scheme 1.5).[19]




**Scheme 1.5**

After screening a variety of different phosphoramidite ligands, they concluded that Feringa's ligand **23**[20] was the most effective with both cyclic and acyclic ketones. The catalytic system could be applied to the conjugate addition of both $Me_3Al$ and $Et_3Al$ and provided high yields of the desired products with good to excellent levels of enantioselectivity.

In the continued search for simpler ligands, Alexakis *et al* have also recently published a study on the hemilabile heterobidentate ligand BINPO **31** in the metal-catalysed 1,4-addition reaction (Scheme 1.6).[21] It was hypothesised that the coordination of the soft phosphorus atom to the copper catalyst and the hard oxygen to an aluminium or zinc species would result in a highly organised transition state.




**Scheme 1.6**

In the event, this ligand proved to be unsuitable for use in conjunction with $Et_2Zn$, as low levels of enantiomeric excess were observed. Conversely, the screenings with $Me_3Al$ met with greater success and enantioselectivities of over 70% were generally achieved with a range of both cyclic and acyclic ketones; although trials with $Et_3Al$ resulted in lower yields and enantioselectivities. Isolated yields of the conjugate products were frequently low and this was attributed to the competing polymerisations of the intermediate aluminium enolates. The group asserted that the heterobidentate nature of the BINPO ligand was essential for the high levels of stereoselectivity observed. They evidenced this claim with the fact that the closely related homobidentate BINAP was a poor ligand for inducing enantioselectivity in conjugate additions.

In 2007, Woodward and co-workers published a set of investigations they had undertaken on a library of sugar–phosphite–oxazoline and phosphite–phosphoramidite ligands.[22] Inspired by earlier literature work in the area, they systematically screened two sugar-based libraries of phosphite–phosphoramidite and phosphite–oxazoline ligands to explore the effect of altering the electronic and steric properties of these ligands (Fig 1.2).

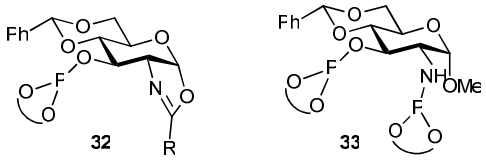
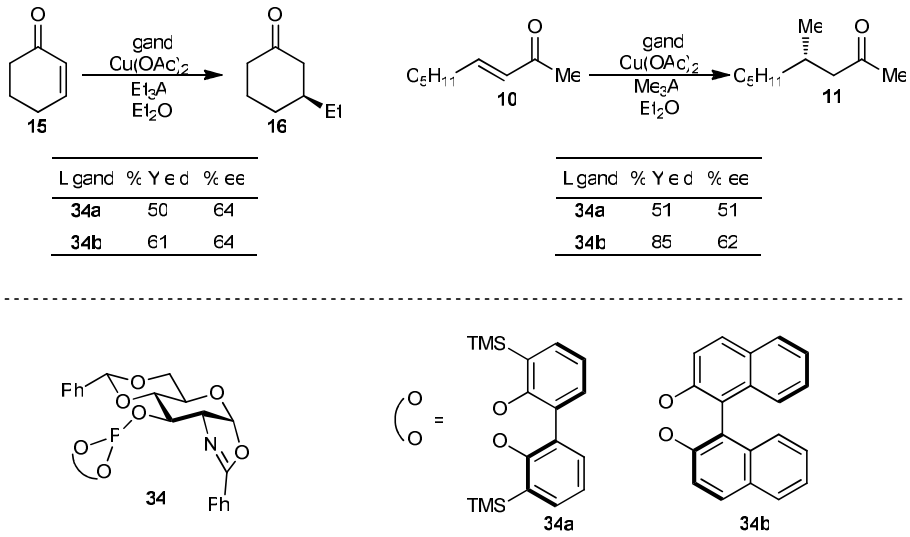



**Figure 1.2**

The libraries were based around a 4,5-*O*-protected glucopyranoside backbone with a phosphite moiety at the C3 position and either an oxazoline or phosphoramidite group attached, as shown in Fig 1.2. Selected results have been shown for the two model substrates **15** and **10**, in the presence of the most successful ligands (**34a** and **34b**, Scheme 1.7) that these libraries produced.

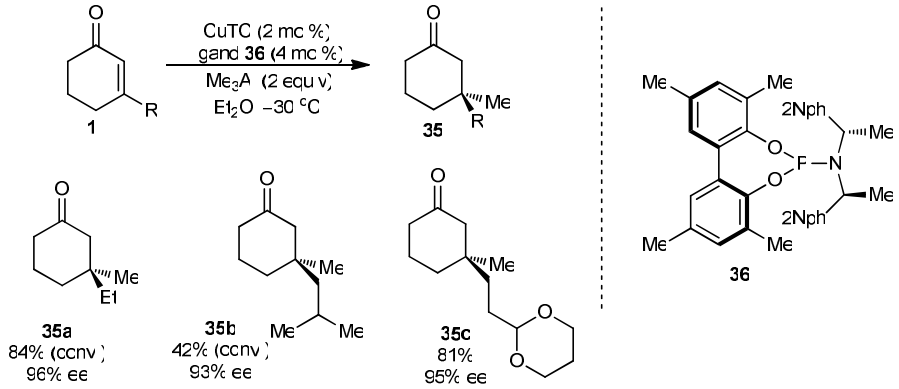



**Scheme 1.7**

The paper concluded that for cyclic enone substrates, the enantioselectivity of the step was significantly affected by substitutions and configuration at the biaryl phosphite moiety, whereas the reaction was largely unaffected by changes to the oxazoline moiety. It was reported that replacing the oxazoline with the phosphoramidite group had a deleterious effect on both the yield and ee of the reaction. This latter observation was repeated for the acyclic enone but in this case, changes at both the biaryl phosphite and the oxazoline moieties had significant effects on the yield and enantioselectivity of the reaction. It is important to note that, despite extensive screening, this library did not produce any ligands capable of delivering superior levels of asymmetric induction to those systems previously reported.

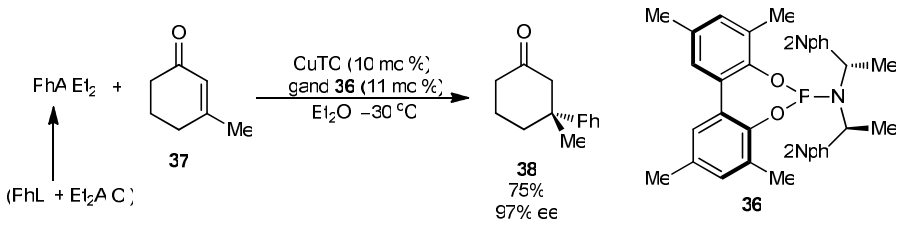
Despite their dominance in the field of enantioselective conjugate additions, the copper-catalysed conjugate addition of $Et_2Zn$[2] and the rhodium-catalysed conjugate addition of aromatic boronic acids[4] have certain critical shortcomings that have not yet been overcome. A notable example is the asymmetric synthesis of quaternary centres, which are problematic due to the low reactivity of β-trisubstituted enones. Alexakis *et al* reasoned that the stronger Lewis acidity of the organoaluminium reagents would effect a better activation of these sterically hindered substrates compared with the corresponding zinc reagents. Their hypothesis was happily

fulfilled and a catalytic system was developed for the construction of stereogenic quaternary centres *via* the conjugate addition of $Me_3Al$ (Scheme 1.8).[23]




**Scheme 1.8**

A range of β-trisubstituted cyclic enones successfully underwent the conjugate addition with exceptionally high enantiomeric excess, although no acyclic enones were reported. A full paper in 2007 described further optimisation of the catalytic system and demonstrated its compatibility with even more demanding substrates, including β-trisubstituted cyclopentenones.[24] Additionally, the same type of catalytic system was successfully applied to the construction of aryl-substituted quaternary centres using *in situ* prepared aryl aluminium reagents (Scheme 1.9).[25]




**Scheme 1.9**

Previously there had been no general method for the introduction of a wide range of aryl groups onto a β-trisubstituted enone but the preparation of the aryl alanes *via* the transmetallation from an aryl lithium circumvented this problem and provided an extensive range of aryl alanes. Under these conditions the aryl group was transferred preferentially and the competing ethyl addition was not observed.

In 2006, the same group also described an *N*-heterocyclic carbene ligand for the copper-catalysed asymmetric conjugate addition of $Et_3Al$ to 3-methylcyclohex-2-enone.[26] The reaction went to 94% conversion but only with a relatively low enantiomeric excess of 54%. This type of ligand was found to be more successful with Grignard reagents which were the main focus of the paper.

Hoveyda and co-workers have also been working on the problematic issue of the asymmetric synthesis of quaternary stereocentres using conjugate addition reactions. Their main objective was the notoriously challenging substrate class of β-substituted cyclopentenones. They applied the group's recently developed bidentate *N*-heterocyclic carbene complexes to the problem, in conjunction with a copper triflate catalyst (Fig 1.3).[27]

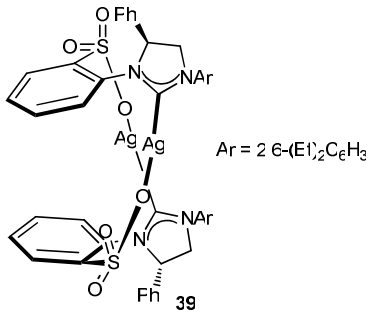
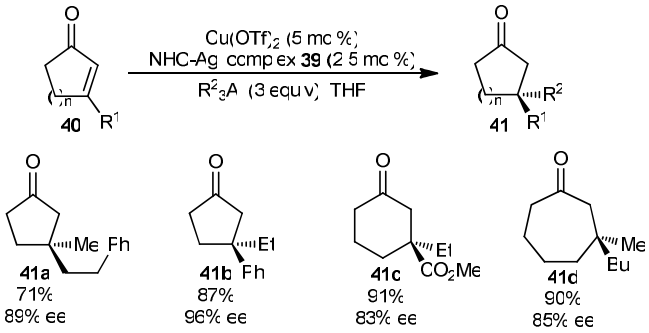



**Figure 1.3**




**Scheme 1.10**

The methodology was successful in promoting the conjugate addition of both trialkylaluminium reagents and aryl alanes to a variety of β-trisubstituted cyclopentenones and larger ring size substrates (Scheme 1.10). The major drawback

of the system is that the complex ligands required are not yet commercially available and have to be prepared in-house in five to six steps.

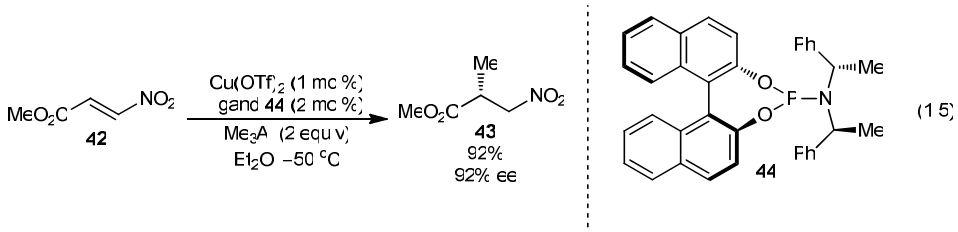
In conclusion to this section, it is only relatively recently that the enantioselective conjugate addition of trialkylaluminium reagents to α,β-unsaturated ketones has become more widely studied. Initially the asymmetric variants of this conjugate addition were less successful than the more common copper-catalysed conjugate additions of $Et_2Zn$ and rhodium-catalysed additions of aromatic boronic acids. In early studies, the ligands required for respectable levels of asymmetric induction were complex; fortunately the advent of the commercially available Feringa's ligand has meant that a high degree of enantiomeric excess can now be obtained for the conjugate addition of trialkylaluminiums to enones using relatively simple phosphoramidite ligands. For the more challenging and less reactive substrates such as β-trisubstituted cyclopentenones, novel catalytic systems have been reported, although the complexity of the ligands required will currently hamper rapid development in this area.

### 1.1.3 Conjugate Addition to Other α,β-Unsaturated Acceptors

The studies discussed previously have been concerned with the metal-catalysed conjugate addition of trialkylaluminium reagents to enone-type substrates. The utility of the transformation would be greatly enhanced if it could be applied to a wider range of α,β-unsaturated acceptors. In this way, we potentially have access to a rich array of new reactions in the area of conjugate additions of trialkylaluminium reagents.

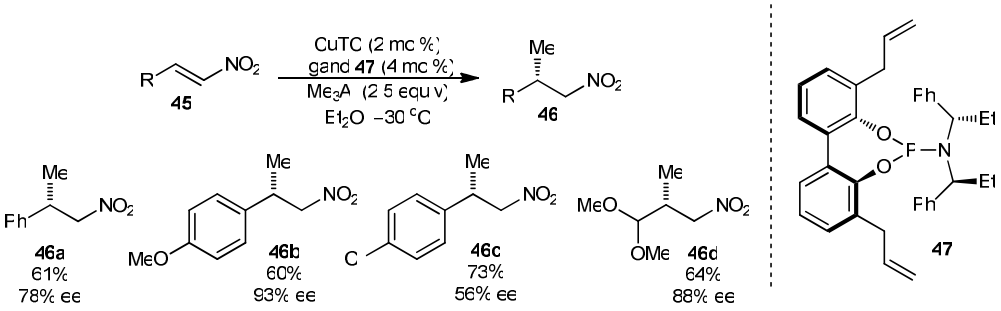
#### *Conjugate Addition to Nitroalkenes*

During studies on β-amino acids, workers at ChiroBlock were investigating the conjugate addition of a methyl group to nitroacrylates and their derivatives (eq 1.5).[28]




After a small amount of optimisation including variation of ligand, solvent and temperature they were able to synthesise the desired product on a 200 g scale. However, they did report that prior reduction of the copper catalyst with a small amount of $Et_2Zn$ was essential to achieve reproducible results. This report appears to be the first literature example of a conjugate addition of a trialkylaluminium reagent to a non-enone α,β-unsaturated substrate. Interestingly, the reaction was highly selective and no conjugate addition was observed at the β-position of the ester group of these two-fold Michael acceptors.

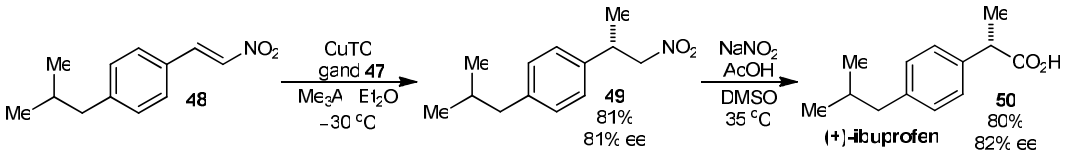
Alexakis and Polet reported the asymmetric conjugate addition of $Me_3Al$ to simple nitroalkenes in 2005 (Scheme 1.11).[29] Previous work had involved phosphoramidite ligands in the copper-catalysed conjugate addition of $Et_2Zn$ to nitrostyrenes.[30] However, attempts to extrapolate this protocol to $Me_2Zn$ were unsuccessful due to the lower reactivity of $Me_2Zn$, and therefore efforts were directed towards an aluminium-based system.




**Scheme 1.11**

A range of acyclic conjugate addition products were obtained in moderate to high yields and enantioselectivities; superior results to those obtained with $Me_2Zn$. It was also observed that electron-donating groups on the aromatic ring increased the

enantioselectivity of the reaction whereas electron-withdrawing groups had the opposite effect. This methodology was validated in the synthesis of (+)-ibuprofen as illustrated in Scheme 1.12.

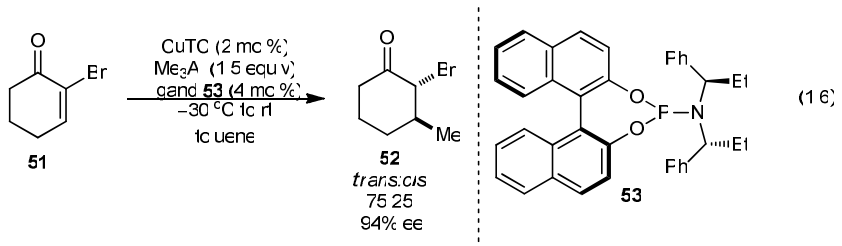



**Scheme 1.12**

The copper-catalysed conjugate addition of $Me_3Al$ to the nitroalkene **48** was achieved in 81% ee and a functional group manipulation provided the carboxylic acid (+)-ibuprofen **50**.

### *Conjugate Addition to a-Halo Enones*

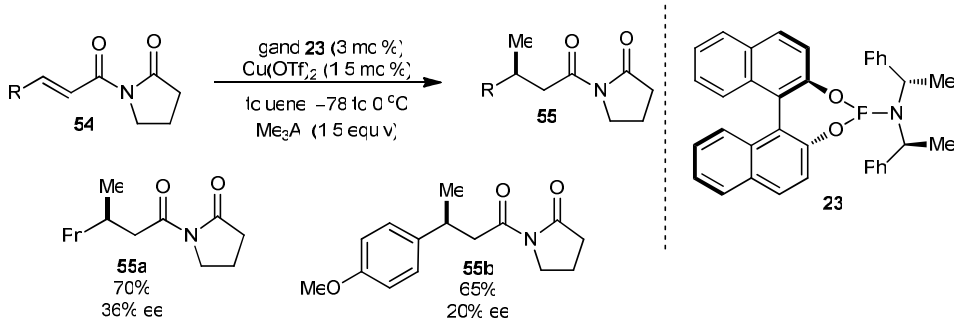
In addition, Alexakis reported one example of enantioselective conjugate addition of $Me_3Al$ to an α-halo enone system in 2006 (eq 1.6).[31]




This copper-catalysed reaction had been optimised for the addition of $Et_2Zn$ and those results formed the main body of the paper, but the methodology was also successfully applied with the aluminium reagent. The reaction had a high ee of 94% and a reasonable *trans:cis* ratio (75:25).

### *Conjugate Addition to Acyclic α,β-Unsaturated Imides*

Pineschi *et al* reported the enantioselective conjugate addition of $Me_3Al$ to aliphatic carboxylic acid derivatives in 2006 (Scheme 1.13).[32]




**Scheme 1.13**

The catalytic system comprising of a copper triflate catalyst and the commercially available phosphoramidite ligand **23** gave exceptionally high enantioselectivities for the addition of $Et_2Zn$ to these imides. However, only two examples involving the addition of $Me_3Al$ were reported, both with very modest levels of asymmetric induction.

### *Conclusions*

The paucity of literature on the conjugate additions of trialkylaluminium reagents to other α,β-unsaturated acceptors indicates that it is a non-trivial transformation. Significantly, in relation to the proposed project (*vide infra*), there are no previous examples of metal-catalysed conjugate additions of trialkylaluminium reagents to α,β-unsaturated amides.

## 1.2 Tandem Conjugate Addition–Aldol Reactions

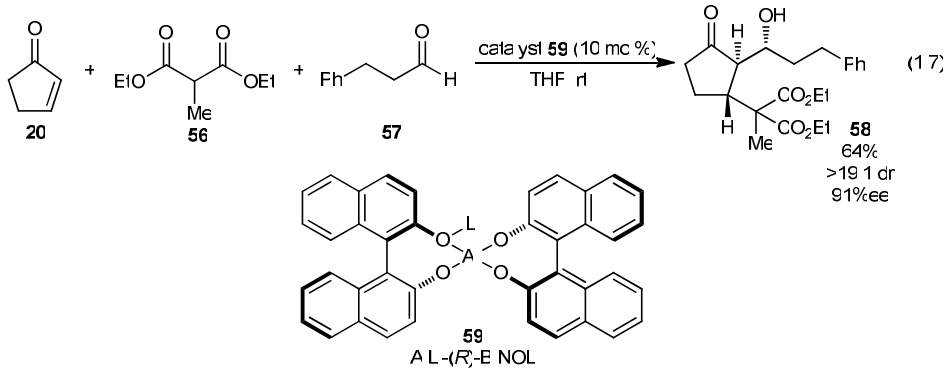
The tandem conjugate addition–aldol reaction facilitates the formation of multiple carbon–carbon bonds in a single step, potentially allowing a substantial increase in

molecular complexity with great stereocontrol. For the purposes of this review we will examine those reactions in which a carbon-based nucleophile is involved in the conjugate addition step, concentrating on metal-catalysed, organocatalysed and radical-mediated transformations.

### 1.2.1 Metal-Catalysed Reactions

#### *Heterobimetallic Catalysis*

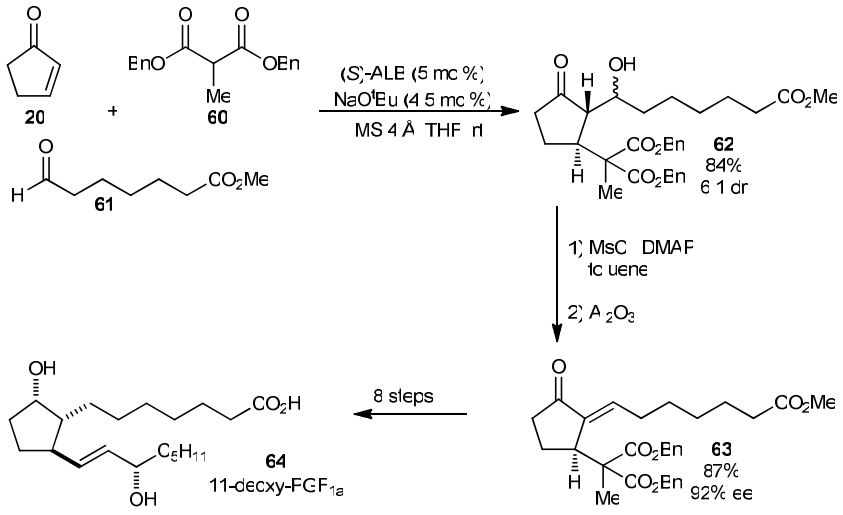
Heterobimetallic catalysis can sometimes offer advantages over traditional catalytic systems based on one metal because of positive cooperation between different metals. In fact it was one such example by Shibasaki and co-workers that became the very first report of a catalytic asymmetric tandem Michael–aldol reaction (eq 1.7).[33]




(1.7)

The AlLi-(*R*)-BINOL complex **59** (or (*R*)-ALB) is able to deprotonate the diethyl methylmalonate **56** to give the corresponding lithium enolate. The coordination of the cyclopentenone **20** to the aluminium centre activates the enone and also fixes its position, resulting in the high facial selectivity that is observed in the subsequent conjugate addition reaction with the lithium enolate. The heterobimetallic complex **59** is one of the few catalysts that allowed the subsequent aldol reaction to take place; other lanthanum-based heterobimetallic catalysts, effective for simple conjugate additions, did not allow the three-component coupling to occur. It was thought that the aluminium enolate intermediate was able to react with the aldehyde faster than

protonation was able to take place. The broad synthetic utility of this methodology was demonstrated in the synthesis of the biologically active 11-deoxy-$PGF_{1\alpha}$ (Scheme 1.14).[34]

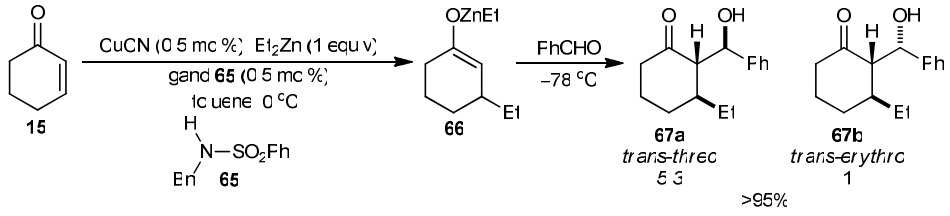



**Scheme 1.14**

Initially the conjugate addition–aldol reaction is followed by a dehydration reaction to give compound **63** with exceptionally high enantioselectivity. The target compound, 11-deoxy-$PGF_{1\alpha}$, is obtained after eight further steps.

### *Copper-Catalysed Reactions*

The earliest example of a copper-catalysed conjugate addition–aldol reaction was described by Noyori and co-workers in 1996 (Scheme 1.15).[35]

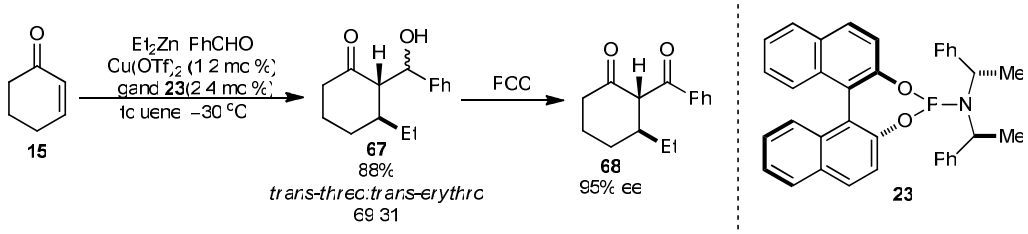



**Scheme 1.15**

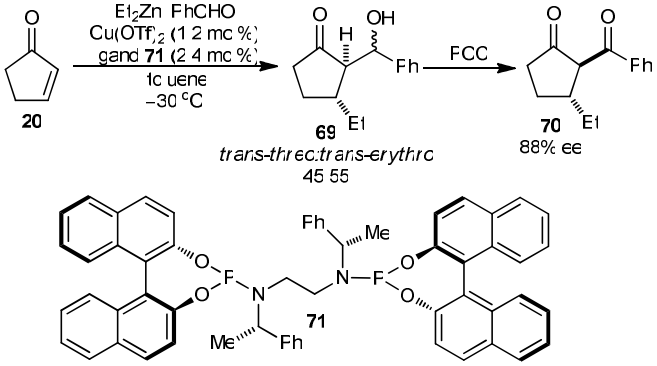
The conjugate addition of $Et_2Zn$ was catalysed by a copper(I)-*N*-monosubstituted sulfonamide species and the resultant zinc enolates were trapped with benzaldehyde.

A mixture of the *trans-threo* and *trans-erythro* products, containing three contiguous stereocentres, were obtained with reasonable stereoselectivity.

In subsequent years, Feringa and co-workers reported an asymmetric protocol using chiral phosphoramidite ligand **23**[36] for the tandem conjugate addition–aldol reaction with 2-cyclohexenone (Scheme 1.16) and ligand **71**[37] for the equivalent reaction with 2-cyclopentenone (Scheme 1.17).



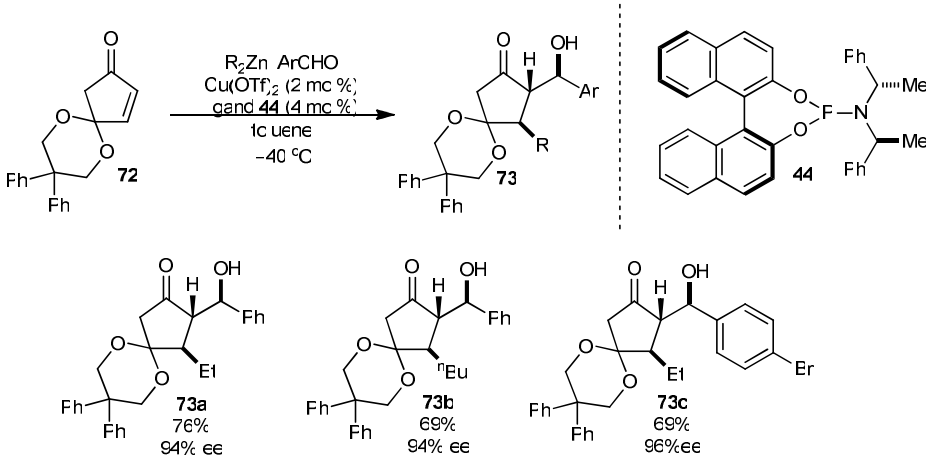

**Scheme 1.16**




**Scheme 1.17**

In both cases the aldol products were oxidised prior to the measurement of enantioselectivity and this neatly removed the issue of low diastereoselectivities.

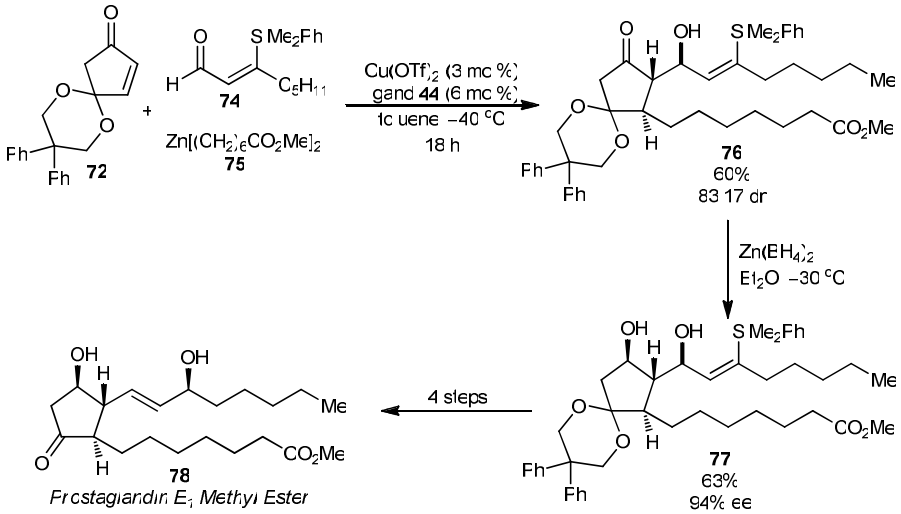
Feringa's group went on to report studies on the tandem reaction of monoprotected cyclopenten-3,5-dione monoacetals in 2001 (Scheme 1.18).[38]




**Scheme 1.18**

A number of examples were described and the reaction conditions yielded exclusively the *trans*-substituted cyclopentanones in moderately high yields. Good stereocontrol was observed in the reaction; diastereomeric ratios of higher than 95:5 were obtained for the β-hydroxyketones and exceptionally high levels of enantioselectivity were reported.

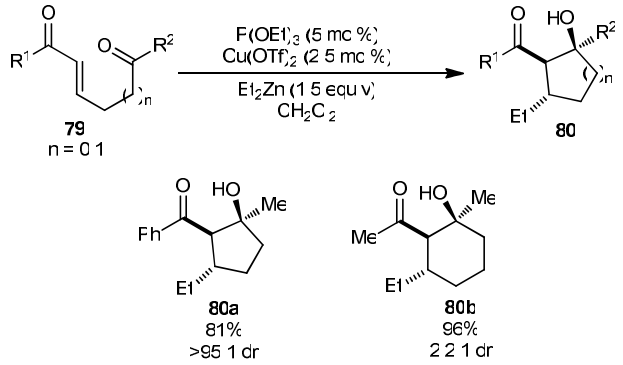
This new methodology was utilised to great effect in the total synthesis of the polyoxygenated fatty acid (-)-prostaglandin $E_1$ methyl ester (Scheme 1.19).[39]




**Scheme 1.19**

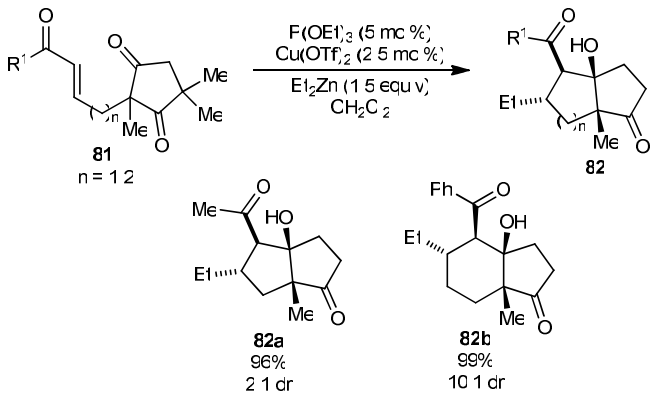
The key multicomponent coupling step was effective, providing the aldol product **76** in a reasonable yield with respectable diastereoselectivity.

An intramolecular variant of this transformation by Krische describes the first use of ketones (in addition to nitriles and esters) as the electrophilic trap in a domino conjugate addition–aldol reaction (Scheme 1.20).[40]



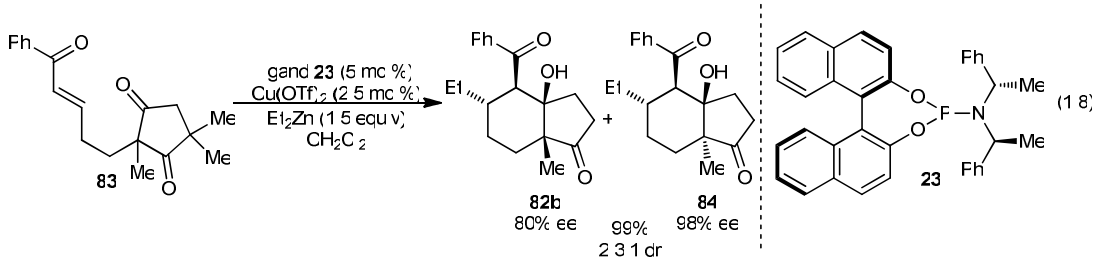

**Scheme 1.20**

The keto–enone precursors gave cyclisation products in exceptionally high yields, although the diastereoselectivity of the reaction was variable. The group additionally reported the alkylative aldol reaction of a set of enone substrates containing 1,3-diones as the electrophilic trap (Scheme 1.21). These precursors provided bicyclic products containing up to four contiguous stereocentres with reasonable diastereoselectivities.

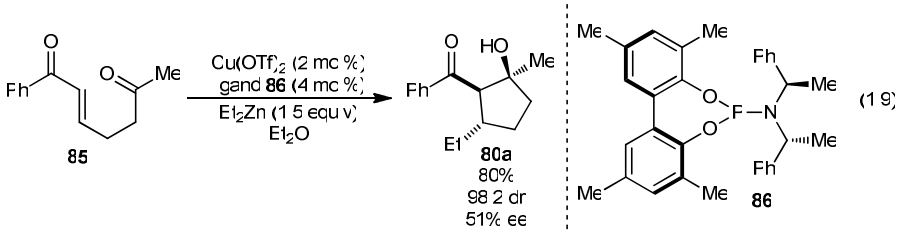



**Scheme 1.21**

One asymmetric example was reported using a chiral phosphoramidite ligand in place of the triethylphosphite; high levels of asymmetric induction were observed although the diastereoselectivity was reduced (eq 1.8).



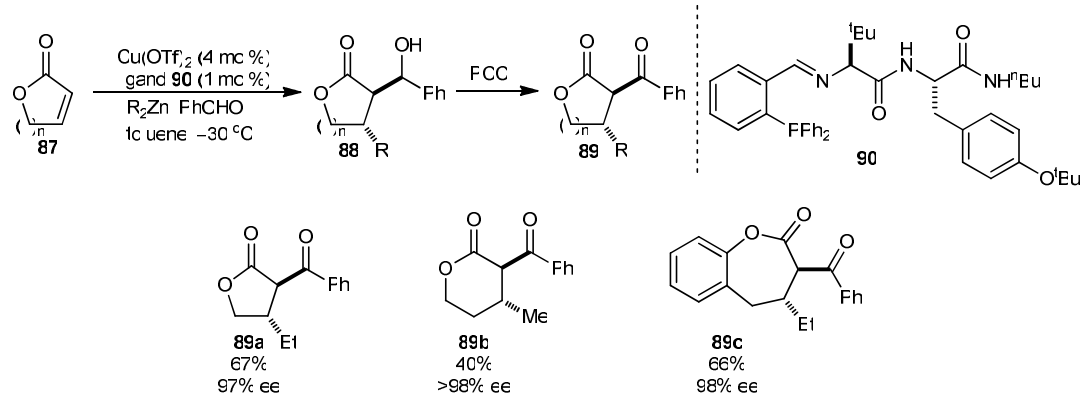

During studies on copper-catalysed enantioselective conjugate addition–trapping reactions, Alexakis and Li reported a similar intramolecular conjugate addition–aldol transformation (eq 1.9).[41]




In their sole example, the reaction proceeded with exceptionally high diastereoselectivity and low levels of asymmetric induction, which was obtained with a biphenol-based phosphoramidite ligand **86**. It is clear that controlling both the absolute and relative stereochemistry of the products, whilst maintaining high conversions, is a non-trivial matter in this transformation.

The majority of the protocols described thus far utilise an enone as the initial Michael acceptor. Expansion of the substrate scope to include a wider range of α,β-unsaturated acceptors would powerfully enhance the utility of the reaction, as a far greater range of products would be accessible.

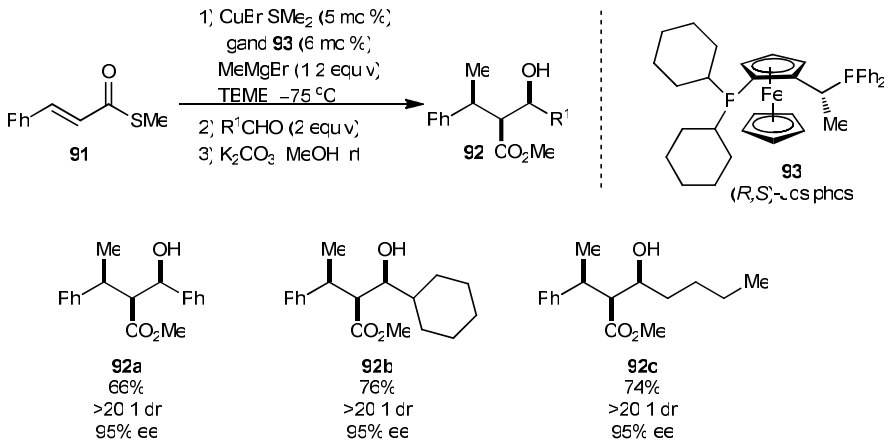
Hoveyda *et al* reported the first general protocol for asymmetric conjugate addition to unsaturated furanones and pyranones using amino acid-based phosphane ligands for the copper-catalysed addition of dialkylzinc reagents (Scheme 1.22).[42]




**Scheme 1.22**

Yields of the conjugate addition product were very low in the absence of the aldehyde, as the intermediate zinc enolate is highly reactive and so can form intermolecular Michael adducts. The aldol products were oxidised *in situ* to the corresponding diketones, which were obtained in reasonable yields with exceptional levels of enantioselectivity.

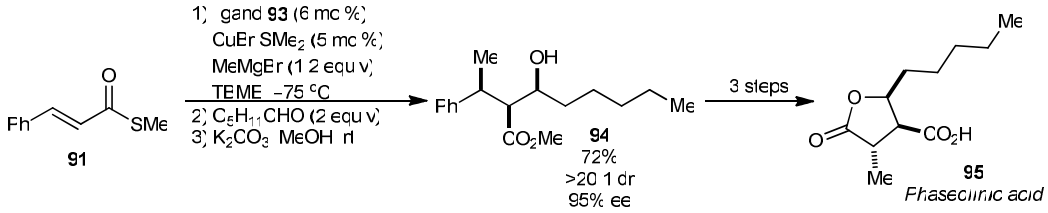
In 2006, Feringa and co-workers reported the first catalytic asymmetric methodology for the tandem conjugate addition–aldol reaction of acyclic substrates using organometallic nucleophiles.[43] The copper-catalysed process employed the Josiphos ligand **93** in conjunction with a Grignard reagent as the carbon-based nucleophile (Scheme 1.23).




**Scheme 1.23**

The tandem aldol products were obtained in good yields and with excellent control of the absolute and relative stereochemistry. A major advantage of this novel system was that the aldol reaction of the more reactive magnesium enolate took place in under a minute at –78 °C. Previous reactions involving zinc species required extended reaction times, often over 24 hours.

Feringa successfully employed these conditions in the first catalytic asymmetric synthesis of phaseolinic acid (Scheme 1.24).[43]

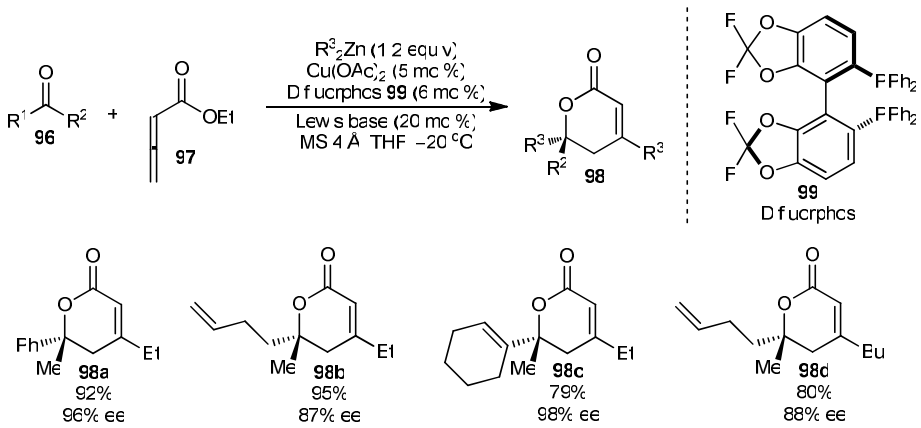



**Scheme 1.24**

The key tandem conjugate addition–aldol reaction in the concise five-step synthesis proceeded in a good yield, with outstanding levels of diastereoselectivity and enantioselectivity.

More recently Shibasaki utilised allenic esters as the initial Michael acceptor in the domino conjugate addition–aldol reaction. The multicomponent assembly of

dialkylzincs, allenic esters and ketones produced highly functionalised γ-lactones containing a quaternary stereocentre in one step (Scheme 1.25).[44]

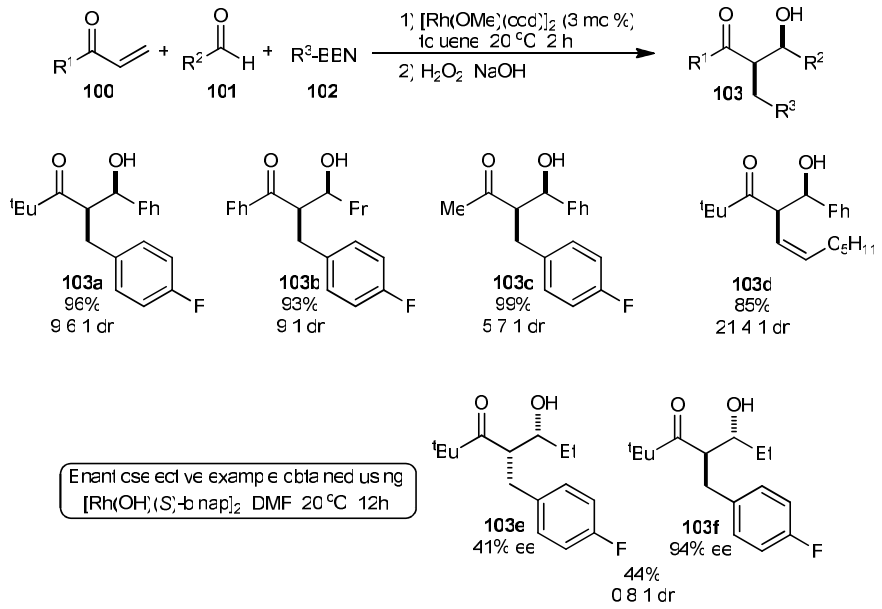



**Scheme 1.25**

During initial screening it was observed that the Lewis base (either DMSO or HMPA) and molecular sieves were essential to obtain high product yields. After the initial conjugate addition reaction, the resultant enolate can either undergo the aldol reaction at the α-position or the desired γ-position. In the absence of the aforementioned additives a significant amount of the kinetic α-aldolate was formed. The group surmised that the combination of molecular sieves and Lewis base has a 'proof-reading' effect and facilitates the retro-aldol reaction of the undesired α-aldolates back to the initial enolate. Conversely, the formation of the γ-aldolates is subsequently followed by lactonisation to irreversibly give the desired γ-lactones.

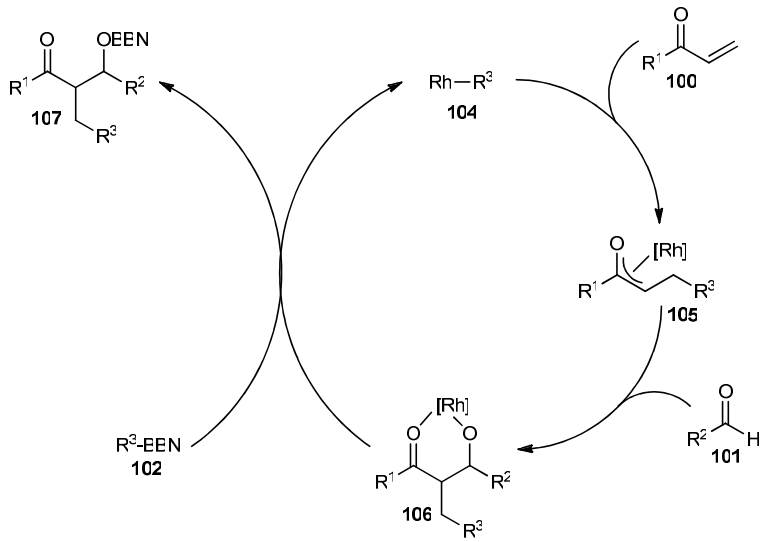
### *Rhodium-Catalysed Reactions*

The group of Hayashi pioneered the use of a rhodium catalyst in the tandem conjugate addition–aldol reaction. They described the three-component coupling of a vinyl ketone, organoborane and an aldehyde (Scheme 1.26).[45]




**Scheme 1.26**

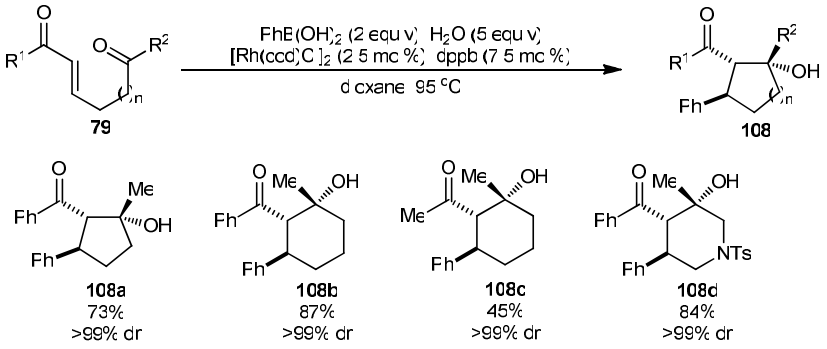
The conjugate addition–aldol products were obtained in excellent yields and with good to high levels of diastereoselectivity. In contrast to the previously described copper-catalysed systems, the rhodium catalyst controls both of the two C–C bond-forming steps. One asymmetric example (Scheme 1.26, **103e** and **103f**) was also reported and the formation of enantiomerically enriched products excluded the possibility of a boron enolate intermediate. The proposed catalytic cycle has been outlined below (Scheme 1.27).




**Scheme 1.27**

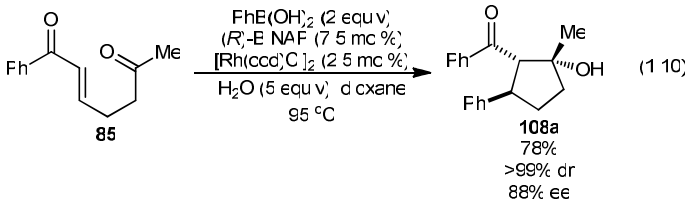
Conjugate addition of the organorhodium species **104** to the vinyl ketone gives the (oxa-π-allyl)rhodium intermediate **105**. Aldol reaction with an aldehyde produces the Rh-aldolate **106** which then transmetallates to liberate the boron aldolate **107** and regenerate the organorhodium intermediate. The high *syn* selectivity is attributed to a Zimmerman-Traxler transition state[46] of the *Z*-Rh enolate at the aldol reaction.

In 2003, a particularly effective protocol for a tandem intramolecular conjugate addition–aldol cyclisation emerged from the laboratories of Krische (Scheme 1.28).[47]



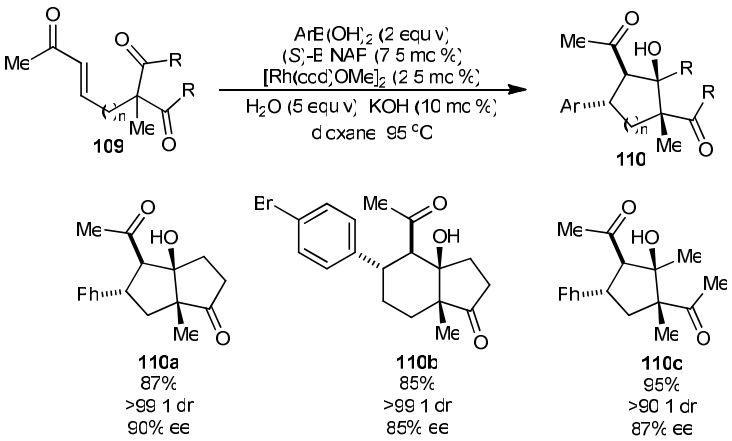

**Scheme 1.28**

The conditions yielded both five- and six-membered ring products containing three contiguous stereocenteres as single diastereomers. The observed stereochemistry was again accounted for by the formation of a *Z*-enolate and a Zimmerman-Traxler[46] transition state. A minimal amount of water was used to ensure that the electrophilic trapping of the rhodium enolate in the aldol cyclisation was faster than enolate protonation. The addition of non-racemic chiral ligands established an enantioselective transformation, which was applied successfully to a number of examples (eq 1.10).




(1.10)

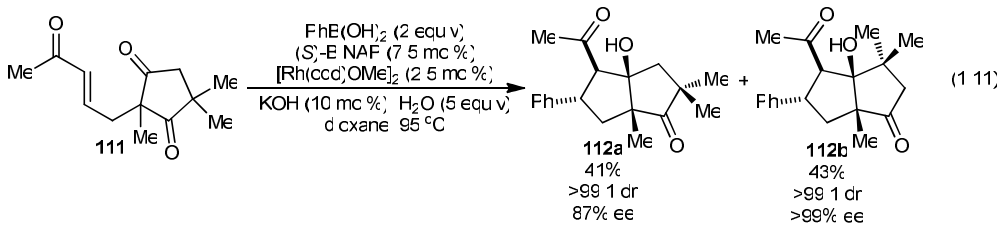
The same group then reported an elegant desymmetrisation reaction using similar conditions and appendant 1,3-diones as the terminal electrophile (Scheme 1.29).[48] In these reactions the conjugate addition–aldol cyclisation of the enone–dione substrates results in the formation of two new C–C bonds and four contiguous stereocentres with a high degree of absolute and relative stereocontrol.




**Scheme 1.29**

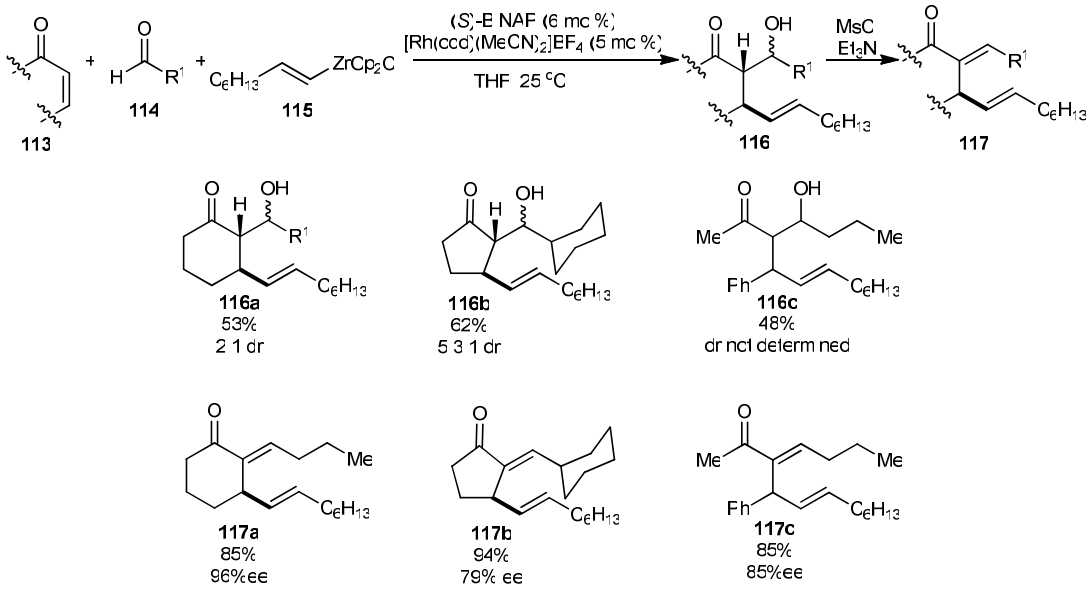
The rhodium enolate generated upon enone carbometallation effectively discriminates between the four diastereotopic π-faces of the appendant dione. Although potentially sixteen stereoisomers could be formed in this step, the high efficacy of the catalytic system provided a single stereoisomer in all cases. A reported limitation was that the system was only effective for α,β-unsaturated ketones, attempts with the corresponding esters resulted in the 1,4-addition but no subsequent cyclisation.

The potential use of this reaction was further demonstrated in the parallel kinetic resolution of racemic enone–diones (eq 1.11).[48]




The absolute stereochemistry of the substrate dictates which of the two non-equivalent carbonyl moieties of the appendant dione participates in the aldolisation step.

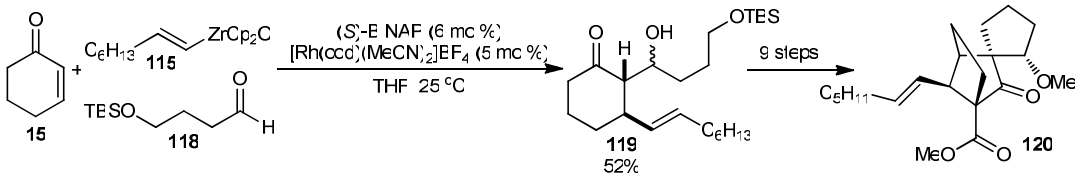
Although most of the rhodium protocols utilise a boron derivative as the organometallic species, Nicolaou explored the conjugate addition–aldol reaction of an alkenylzirconium reagent, during a programme of work directed towards the total synthesis of the marine natural product vannusal A (Scheme 1.30).[49]




**Scheme 1.30**

The methodology was applied effectively to five-, six-, and seven-membered ring enones and one acyclic substrate. The reactions proceeded in moderate yields with reasonable levels of diastereoselectivity, an issue that was removed in a subsequent dehydration step. The proposed mechanism bore marked similarities to Hayashi's analogous boron-based system.[45]

The group harnessed their conditions in the synthesis of a complex spirocyclic moiety **120**, a key synthon for the natural product vannusal A (Scheme 1.31).




**Scheme 1.31**

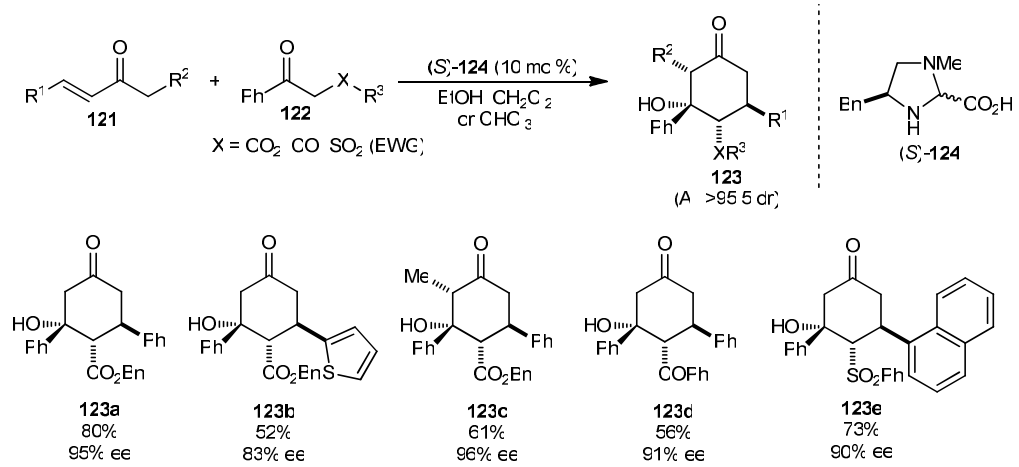
The multicomponent coupling gave the aldol product **119** in a modest yield, although the diastereoselectivity of the reaction was not reported as the substrate was dehydrated at the next stage in the synthesis. A short sequence of transformations allowed the construction of the spirocyclic building block **120**.

### *Conclusions*

The abundance of chiral ligands available for copper and rhodium catalysis has been highly advantageous for the development of the asymmetric tandem conjugate addition–aldol reaction. The rhodium-catalysed conjugate addition–aldol reaction offers a complementary alternative to the analogous copper-catalysed transformation, in that the carbon-based nucleophile that adds to the β-position of the initial Michael acceptor is an aromatic or alkenyl group rather than an alkyl group. Unfortunately, in terms of substrate scope, both systems are limited to α,β-unsaturated ketones as the initial Michael acceptor.

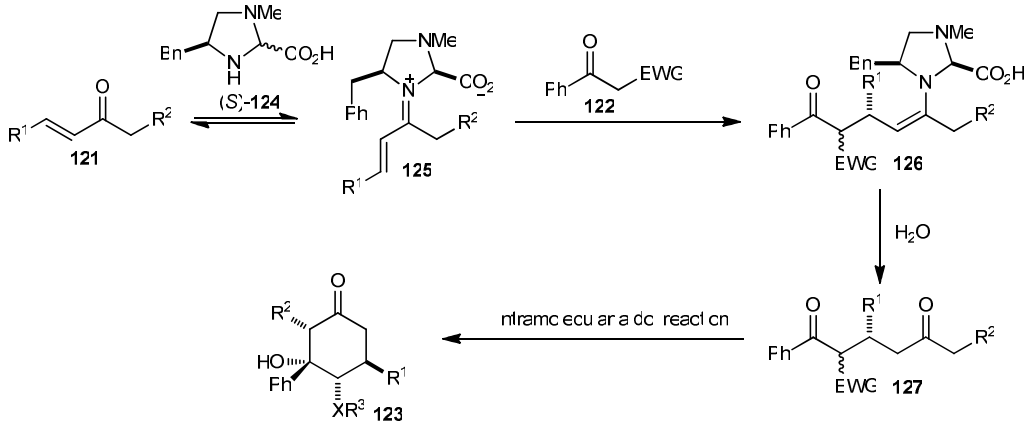
## 1.2.2 Organocatalytic Reactions

Jørgenson's group reported the first asymmetric organocatalytic domino Michael–aldol reaction in 2004. The highly diastereoselective reaction of α,β-unsaturated ketones with β-ketoesters,[50] β-diketones[51] and β-ketosulfones[51] was catalysed by an imidazolidine catalyst derived from phenylalanine (Scheme 1.32).




**Scheme 1.32**

The optically active cyclohexanone products contained up to four contiguous stereocentres and precipitated from the reaction mixture, circumventing the use of column chromatography. The proposed mechanism for this transformation is outlined in Scheme 1.33.



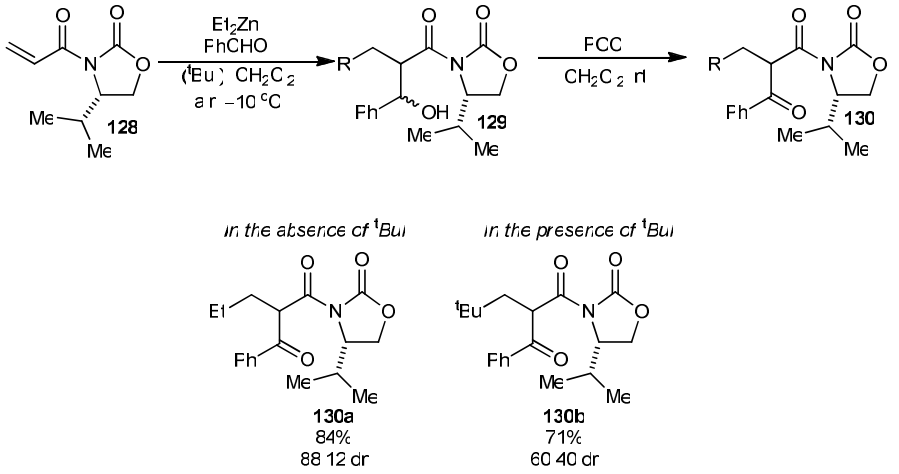

**Scheme 1.33**

It was postulated that the imidazolidine catalyst has three major roles in the reaction: activation of the Michael acceptor by iminium ion formation, generation of the active carbon nucleophile *via* deprotonation of the β-keto substrate **122** and as a base in the final intramolecular aldol cyclisation.

From a green chemistry perspective an organocatalytic process is generally more attractive than conventional metal-catalysed approaches. The use of potentially toxic metals is avoided, the catalysts are usually cheaper and conditions milder. The use of organocatalytic chemistry for the tandem conjugate addition–aldol has yielded some elegant results but the expansion of the substrate scope and the reduction of the currently extended reaction times (>100 h) remain a challenge for the future.

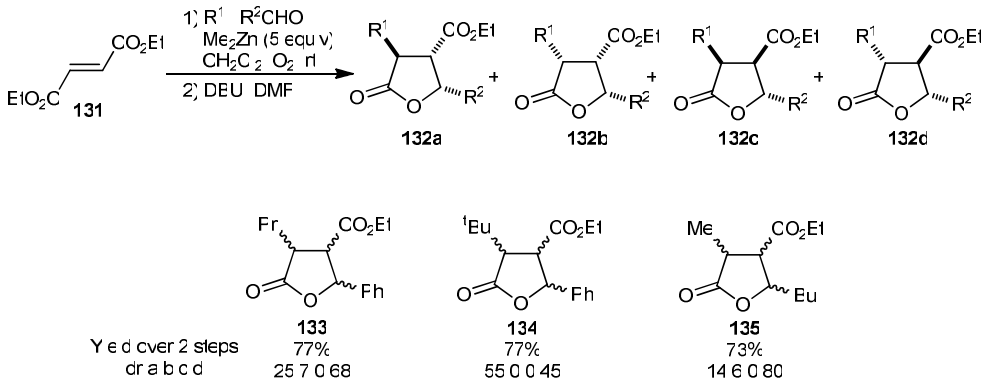
### 1.2.3 Radical-Mediated Reactions

In recent years radical-mediated transformations have emerged as a new subset of the conjugate addition–aldol reaction. Bertrand and co-workers were the first to describe a $Et_2Zn$-mediated addition of alkyl radicals to *N*-enoyloxazolidinones in the presence of oxygen, which was followed by an aldol reaction (Scheme 1.34).[52]



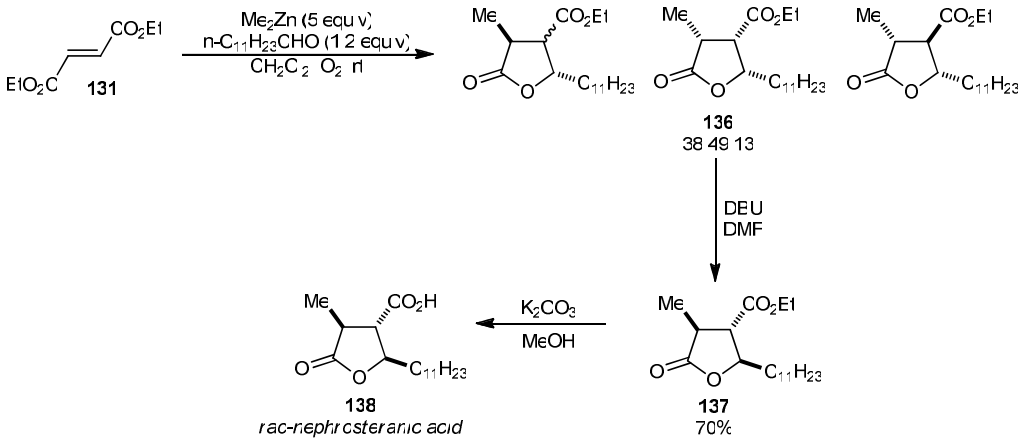

**Scheme 1.34**

In the absence of *tert*-butyl iodide the ethyl adduct was formed, conversely when it was present in the reaction mixture, a *tert*-butyl radical added to the β-position of the Michael acceptor. The group also obtained di- and trisubstituted γ-lactones from fumaric or maleic acids using the same methodology (Scheme 1.35).[53]



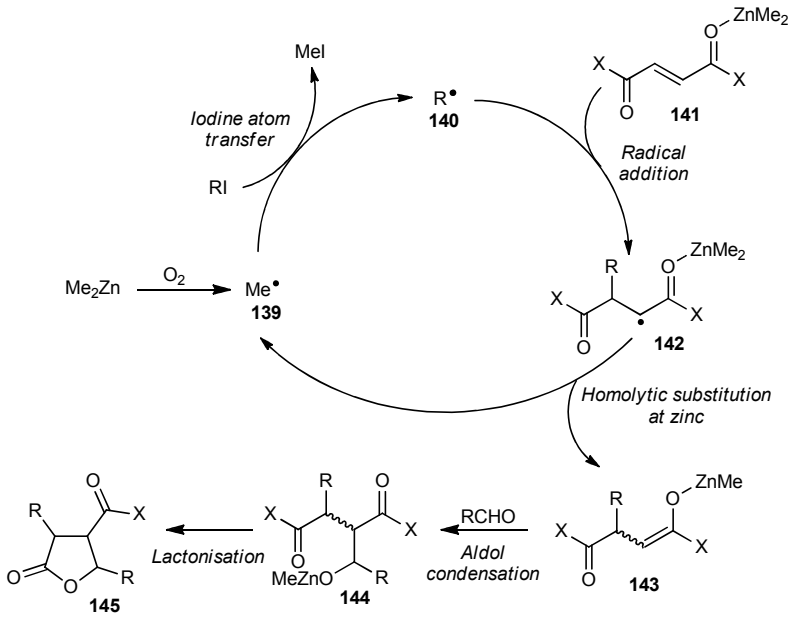

**Scheme 1.35**

A conjugate radical addition, aldol reaction and lactonisation result in the observed products. The use of $Me_2Zn$ in place of $Et_2Zn$ allowed a greater range of alkyl radical precursors. The diastereoselectivity of the reaction was not high, in most cases four diastereomers were observed, this was improved in most cases *via* epimerisation of the enolisable centres. The methodology enabled the group to complete a racemic synthesis of nephrosteramic acid (Scheme 1.36).




**Scheme 1.36**

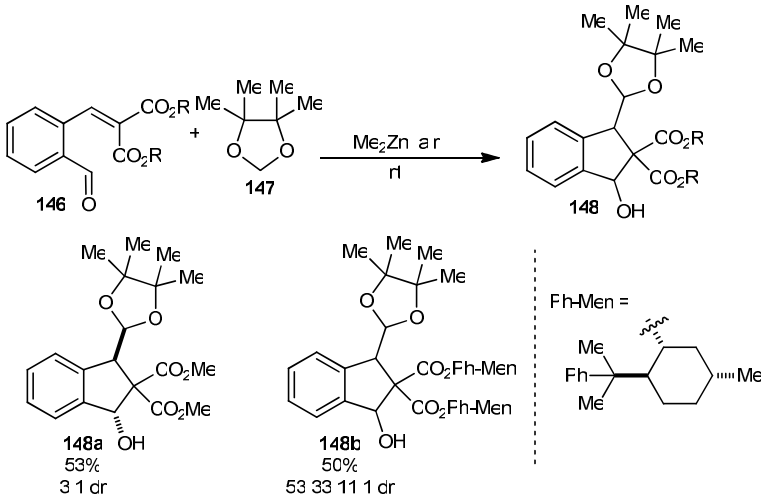
Investigations revealed the reaction went *via* a radical-polar crossover mechanism (Scheme 1.37).[54]




**Scheme 1.37**

Initially an iodine atom transfer to the methyl radical produces the alkyl radical **140**, this can add to the β-position of the $Me_2Zn$-activated Michael acceptor. Homolytic substitution at the dialkylzinc leads to the zinc enolate **143**. An ensuing aldol reaction and lactonisation results in the γ-lactone **145**.

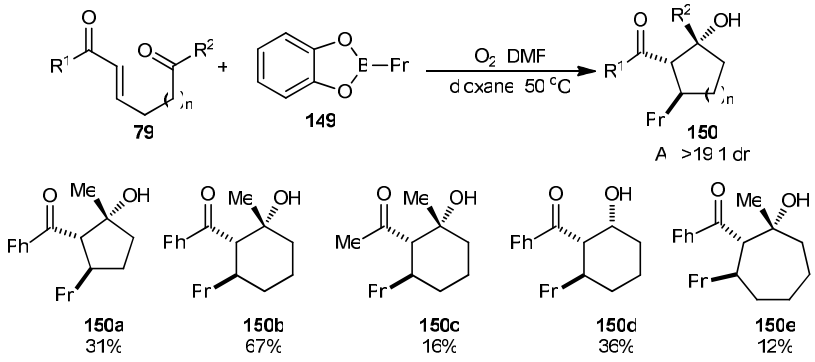
More recently other groups have begun to explore the area of radical-mediated conjugate addition–aldol reactions. Tamioka demonstrated that the $Me_2Zn$-mediated addition of ether radicals could provide tandem conjugate addition–aldol products in one-pot (Scheme 1.38).[55]




**Scheme 1.38**

The tandem reaction provided indane products in moderate yields and diastereoselectivities. The use of bis(8-phenylmenthyl) 2-formylbenzylidenemalonate as a chiral Michael acceptor resulted in the adduct **148b** as a mixture of four diastereomers.

In addition to dialkylzinc-mediated radical transformations, Renaud's group has demonstrated that a *B*-propylcatecholborane-mediated radical addition–aldol cyclisation gives polysubstituted cyclic alcohols in a highly diastereoselective fashion (Scheme 1.39).[56]




**Scheme 1.39**

The reaction to form cyclohexanols was generally effective, although yields were significantly reduced when different ring-sized cyclic alcohols were examined and

when an aldehyde trap replaced the ketone. The radical addition of other *B*-alkylcatecholboranes was not examined and so the scope of the reaction remains limited. After mechanistic studies were carried out, the group surmised that a borane-mediated radical addition of the propyl group is followed by an aldol cyclisation of the boron enolate.

The majority of radical-mediated transformations do not offer huge advantages over the more conventional conjugate addition–aldol reactions in terms of stereoselectivity and substrate scope. In spite of this fact, the recent flurry of publications in this area has demonstrated some effective routes into certain classes of compound and presented some intriguing mechanistic discussions.

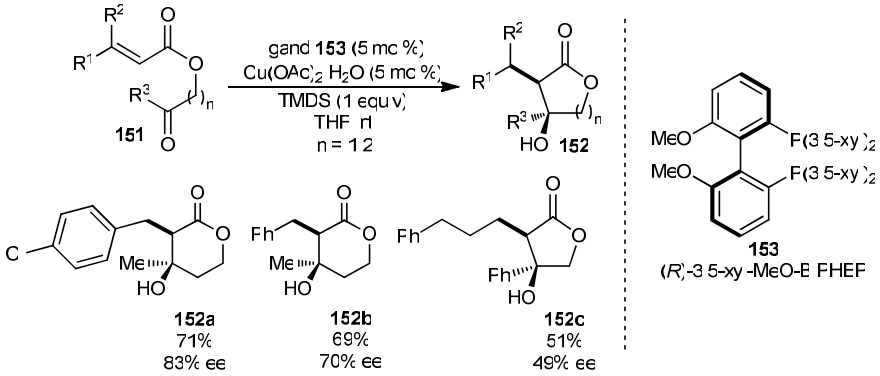
### 1.2.4 Conclusions

There is a significant range of tandem conjugate addition–aldol methodologies available to access an array of relatively complex products from comparatively simple starting materials. Currently the majority of protocols rely on the use of α,β-unsaturated ketones as the initial Michael acceptor; expansion to different types of acceptor substrates will greatly increase the diversity of products accessible *via* this transformation.

# 2.0 Cobalt-Catalysed Alkylative Aldol Reactions Using Trialkylaluminium Reagents

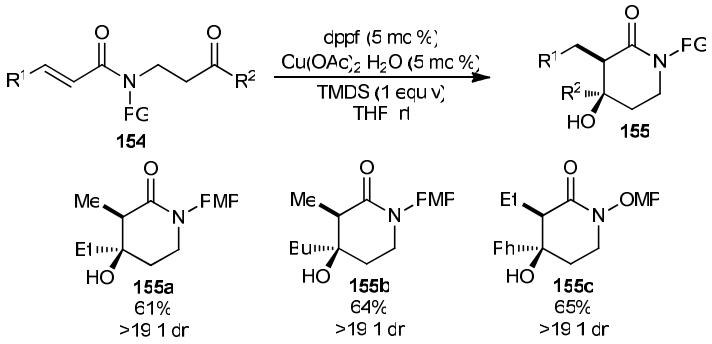
## 2.1 Introduction

Reductive aldol cyclisations have been a key research interest of the Lam Group for a number of years. Our earliest examples comprised of copper-catalysed systems that employed siloxanes as the stoichiometric reductant (Scheme 2.1).[57] The use of chiral phosphine ligands allowed the preparation of enantioenriched β-hydroxylactones.



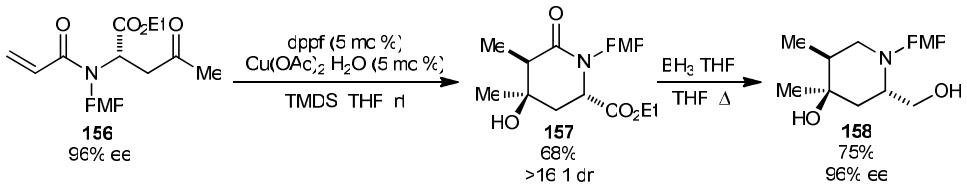

**Scheme 2.1**

Further investigations revealed that the copper-catalysed methodology was effective for substrates containing an amide tether. However, the scope of the reaction was limited to those possessing a hydrogen or a methyl group at the β-position of the α,β-unsaturated amide (Scheme 2.2). [58]



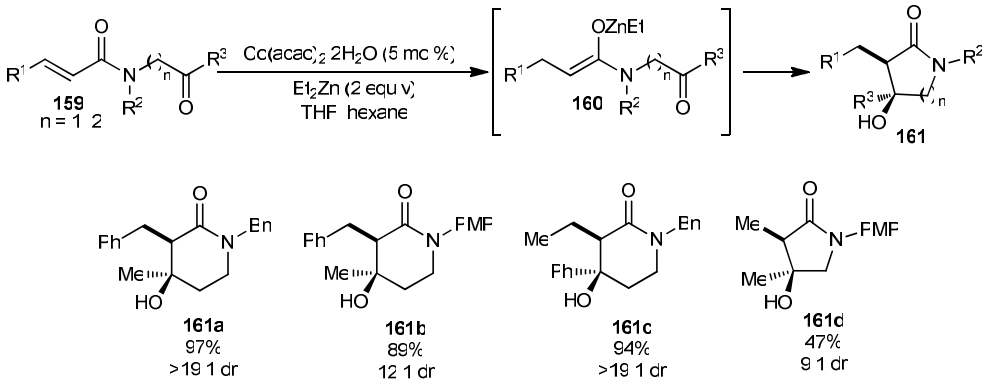

**Scheme 2.2**

The copper-catalysed methodology was used to prepare a series of 4-hydroxypiperidin-2-ones in a highly diastereoselective fashion. The presence of a pre-existing stereocentre in the substrate did not adversely affect the diastereoselectivity of the reductive aldol reaction. A reductive removal of the carbonyl group provided access to piperidine structures, which feature in many biologically active compounds (Scheme 2.3).




**Scheme 2.3**

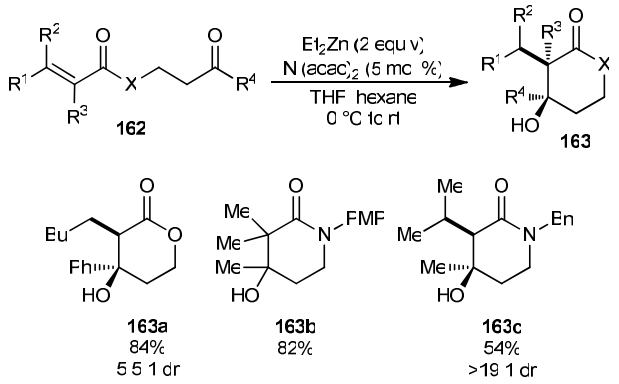
Research in the group was then directed towards a catalytic system that would be effective for a wider range of amide-tethered substrates. The result was a novel system based on a cobalt catalyst, with $Et_2Zn$ acting as the source of hydride (Scheme 2.4).[59]




**Scheme 2.4**

The cobalt-catalysed reaction offered a broader scope for amide-tethered substrates compared to the previously described copper-based method. It was successful with two different nitrogen-protecting groups (-PMP and -Bn), tolerated both aromatic and alkyl substitutions at the β-position, as well as at the tethered ketone and provided a route to both five- and six-membered β-hydroxylactams.

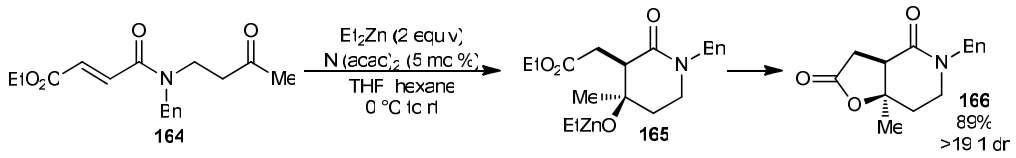
The use of a $Ni(acac)_2$ precatalyst in conjunction with $Et_2Zn$ presented a more general reductive aldol methodology (Scheme 2.5).[60]




**Scheme 2.5**

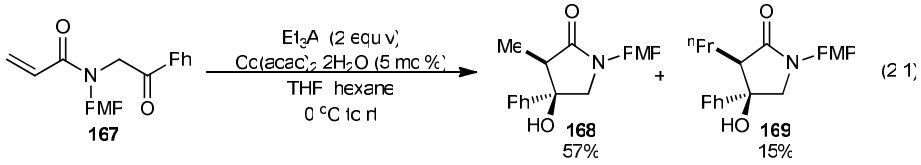
These conditions allowed the expansion of the substrate scope to include ester tethers (**163a**), as well as α-substituted (**163b**) and β,β-disubstituted α,β-unsaturated amides (**163c**). A β-ester substituted α,β-unsaturated amide (**164**) underwent the reductive aldol reaction and subsequently lactonised to give the bicyclic product **166** (Scheme

2.6). Many of these substrates had been inert under the previously reported cobalt conditions or had reacted with poorer reproducibility.

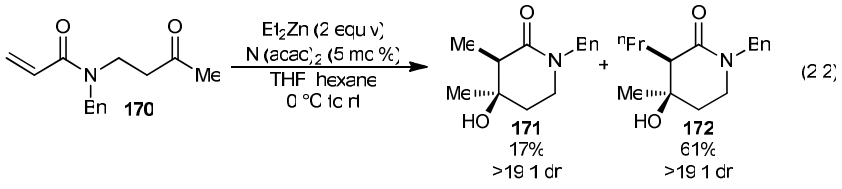



**Scheme 2.6**

During investigations in this area, a competing alkylative aldol reaction was occasionally detected for particular catalyst–reagent–substrate combinations. For example, it was observed that in the cobalt-catalysed reductive aldol reaction, β-unsubstituted acrylamides underwent alkylative aldol cyclisation to a small degree when $Et_3Al$ was used in place of $Et_2Zn$ as the stoichiometric reductant (eq 2.1).[59]




The same phenomenon was observed for β-unsubstituted acrylamides; in the presence of $Ni(acac)_2$ and $Et_2Zn$ the alkylative aldol product **172** was isolated in 61% yield as a single diastereomer (eq 2.2).[60]



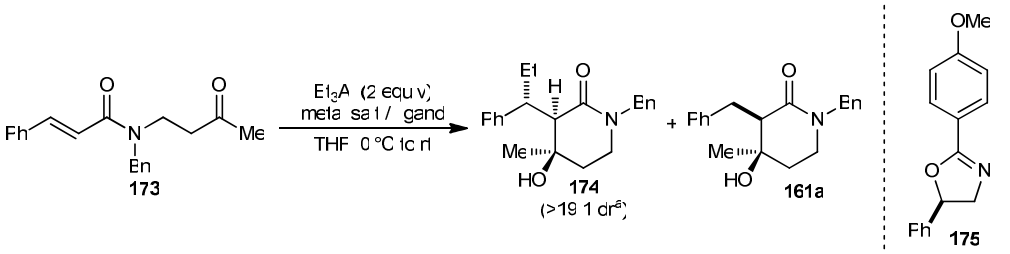

The aim of the proposed programme of work was to exploit these initial results and develop a fully alkylative aldol cyclisation that would complement our existing reductive aldol methodologies. The two previous alkylative aldol reactions were the first examples of conjugate addition of trialkylaluminium reagents to α,β-unsaturated amides and both had proceeded with a high level of diastereoselection (eq 2.1 and

2.2). Conjugate addition of an alkyl group followed by a highly diastereoselective ring closure results in the creation of three new contiguous stereocentres in a single step. An additional goal was to render the protocol enantioselective, as the synthetic utility of the reaction would be further enhanced. Potentially, a relatively complex molecule could be created in one step from simple achiral substrates with a high degree of absolute stereocontrol.

## 2.2 Results and Discussion[61]

### 2.2.1 Optimisation

The development of a complementary alkylative aldol reaction began with the screening of various catalyst and ligand combinations with the model substrate **173** (Table 2.1). Our aim was to favour the formation of the alkylative aldol cyclisation product **174** over the reductive aldol product **161a**, whilst maintaining the high diastereoselectivity that had previously been observed with other substrates (eq 2.1 and 2.2).

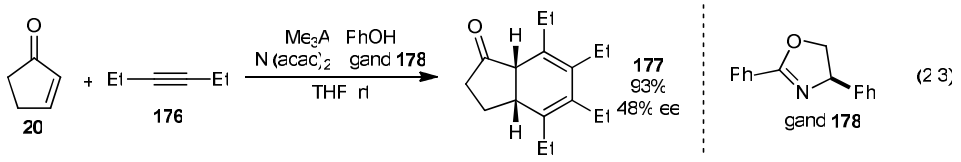



| entry | metal salt (10 mol%) | ligand (10 mol%) | 174:161a [a,b] |
|---|---|---|---|
| 1 | $Ni(acac)_2$ | / | 10:90 |
| 2 | $Ni(acac)_2$ | *rac*-BINAP | 8:92[c] |
| 3 | $(PPh_3)_2NiBr_2$ | / | <5:95[c] |
| 4 | $Ni(acac)_2$ | **175** | 5:95[d] |
| 5 | $CoCl_2$ | $Cy_2PPh$ | 25:75 |
| 6 | $Co(acac)_2{\cdot}2H_2O$ | **175** | >95:5[d] |
| 7 | $Co(acac)_2{\cdot}2H_2O$ | / | >95:5 |

[a] All reactions proceeded to >95% conversion. [b] Determined by $^1H$ NMR analysis of the unpurified reaction mixture. [c] Small quantities of unidentified side products were observed. [d] No enantioselectivity was observed in the reaction.

**Table 2.1**

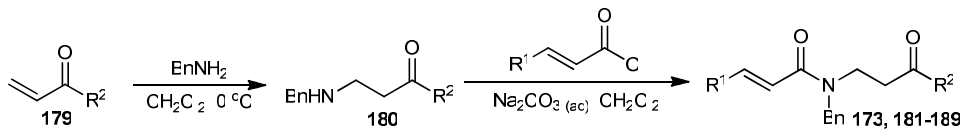
In the first instance, nickel-based precatalysts were examined. In the absence of ligand, a $Ni(acac)_2$ precatalyst resulted in the preferential formation of the reductive aldol product **161a**. The presence of bidentate (entry 2) or monodentate (entry 3) phosphine ligands did not offer any improvements on this selectivity and the reaction conditions continued to favour the reductive aldol product. It was hoped that perhaps the oxazoline ligand **175** would offer a reversal in the selectivity, as Ikeda had successfully applied an oxazoline ligand to enantioselective [2+2+2] cycloadditions using $Ni(acac)_2$ as a precatalyst in the presence of $Me_3Al$ (eq 2.3).[62]

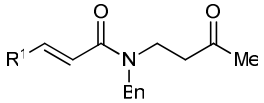
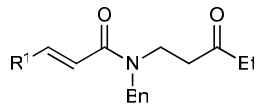


However, the reductive aldol cyclisation remained the pathway of choice in the presence of the oxazoline ligand and so our focus turned to cobalt-based precatalysts. It was found that a combination of $CoCl_2$ and $Cy_2PPh$ (entry 5) resulted in a higher proportion of the desired alkylative aldol product. Moreover, $Co(acac)_2$ gave **174** as the sole product in the presence of the oxazoline ligand **175** (entry 6). To our delight this result was repeated in the absence of any ligand (entry 7) and so these optimised conditions were then applied to a range of different substrates to explore the scope and limitations of the process.

### 2.2.2 Preparation of Cyclisation Precursors

A range of nitrogen-tethered cyclisation precursors, containing an α,β-unsaturated amide and a pendant ketone, were prepared according to the general method shown in Table 2.2.



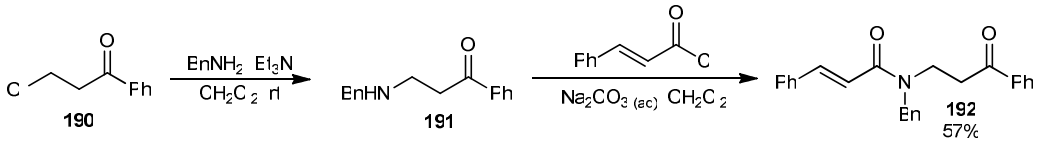

| entry | product | $R^1$ | | yield (%)[a] |
|---|---|---|---|---|
| 1 | | Ph | **173** | 48 |
| 2 | | PMP | **181** | 55 |
| 3 | | 4-methylphenyl | **182** | 38 |
| 4 |  | 4-chlorophenyl | **183** | 37 |
| 5 | | 2-furyl | **184** | 42 |
| 6 | | 2-thiophenyl | **185** | 30 |
| 7 | | OMP | **186** | 47 |
| 8 | | Et | **187** | 49 |
| 9 |  | Ph | **188** | 23 |
| 10 | | PMP | **189** | 34 |

[a] Yield over the two steps.

**Table 2.2**

The cyclisation precursors were obtained in moderate yields over the two steps. The yields of substrates **188** and **189** (entries 9 and 10) were slightly lower than those substrates derived from methyl vinyl ketone (entries 1-8). The purification of these ethyl-substituted ketones **188** and **189** by column chromatography was also more difficult due to co-running impurities.

The substrate **192**,[i] which contains a phenyl-substituted pendant ketone was prepared as described in the literature (Scheme 2.7).[61]

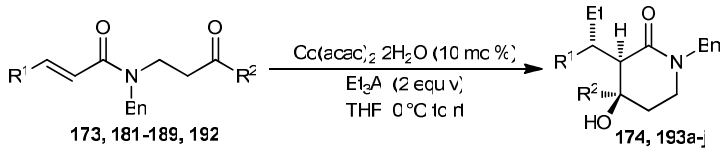


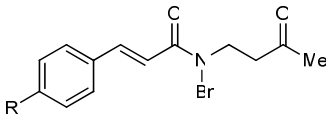
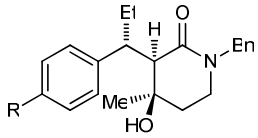
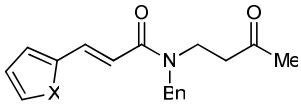
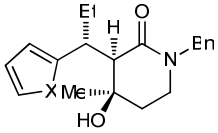
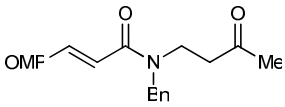
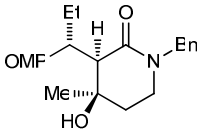
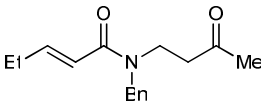
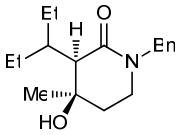
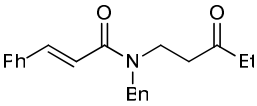
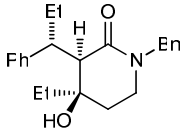
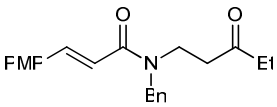
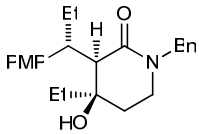
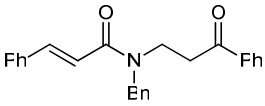
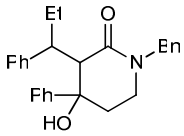

**Scheme 2.7**

### 2.2.3 Cobalt-Catalysed Alkylative Aldol Cyclisations Using $Et_3Al$

The optimised conditions for the alkylative aldol cyclisation using $Et_3Al$ were then applied to a range of α,β-unsaturated amides containing aromatic, heteroaromatic and alkyl groups at the β-position (Table 2.3).

[i] This precursor was synthesised by Dr Pekka Joensuu.




| entry | substrate | | product | | yield[a] (%) |
|---|---|---|---|---|---|
| 1 |  | **173** R = H |  | **174** | 98 |
| 2 | | **181** R = OMe | | **193a** | 91 |
| 3 | | **182** R = Me | | **193b** | 71 |
| 4 | | **183** R = Cl | | **193c** | 48 |
| 5 |  | **184** X = O |  | **193d** | 76 |
| 6 | | **185** X = S | | **193e** | 85 |
| 7 |  | **186** |  | **193f** | 21[b,c] |
| 8 |  | **187** |  | **193g** | 35[d] |
| 9 |  | **188** |  | **193h** | 60 |
| 10 |  | **189** |  | **193i** | 70 |
| 11 |  | **192** |  | **193j** | 52[e,f] |

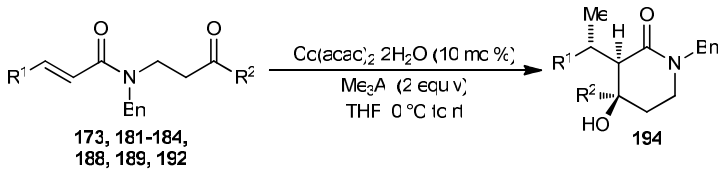
[a] dr >19:1 unless otherwise stated. dr determined by $^1$H NMR analysis of the unpurified reaction mixtures. dr = (major isomer):Σ(other isomers). [b] The reductive aldol product **193k** was obtained in 28% yield. [c] Unreacted starting material (16%) was recovered. [d] Unreacted starting material (35%) was recovered. [e] dr = 1:1 in the crude reaction mixture. Combined yield of both isolated diastereomers. [f] The reductive aldol product **193l** was obtained in 26% yield.

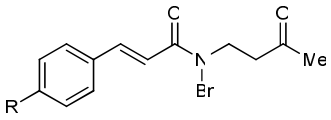
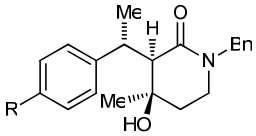
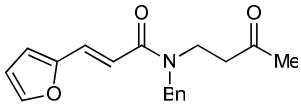
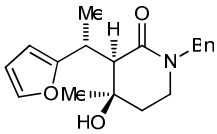
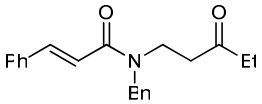
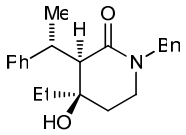
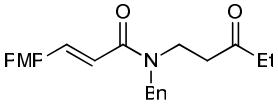
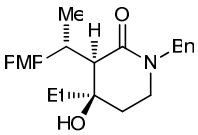
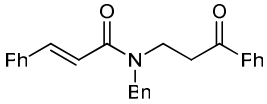
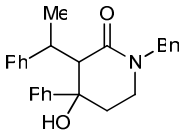
**Table 2.3**

The reaction conditions were well tolerated by substrates containing aromatic (entries 1-4, 7 and 9-11) or heteroaromatic (entries 5 and 6) groups at the β-position of the α,β-unsaturated amide. A study of different substituents on the aromatic ring indicated that more electron-donating groups favoured the reaction (entries 2-4). However, an *ortho*-substitutuent hindered the reaction; the low yield was accounted for by the formation of the reductive aldol product in addition to a poor conversion from the starting material (entry 7). An alkyl group at the β-position of the α,β-unsaturated amide proved to be a less reactive substrate and resulted in a low yield of the desired product (entry 8). In addition, replacement of the pendant methyl ketone with an ethyl ketone was compatible with the reaction conditions (entries 9 and 10). In these substrates the reactions proceeded with uniformly high diastereoselectivities. Unfortunately, a pendant aromatic ketone appeared to have a deleterious effect on the selectivity of the reaction (entry 11). In this case, the alkylative aldol product was obtained as a 1:1 mixture of diastereomers, along with the reductive aldol product.

### 2.2.4 Cobalt-Catalysed Alkylative Aldol Cyclisation Using $Me_3Al$

With a view to expanding this new methodology, we applied our optimised reaction conditions to the alkylative aldol cyclisation of a similar range of substrates using $Me_3Al$ in place of $Et_3Al$ (Table 2.4).




| entry | substrate | | product | | yield[a] (%) |
|---|---|---|---|---|---|
| 1 |  | **173** R= H |  | **194a** | 43 |
| 2 | | **181** R = OMe | | **194b** | 48 |
| 3 | | **182** R = Me | | **194c** | 46 |
| 4 | | **183** R = Cl | | **194d** | 18 |
| 5 |  | **184** |  | **194e** | 40 |
| 6 |  | **188** |  | **194f** | 26 |
| 7 |  | **189** |  | **194g** | 51[b] |
| 8 |  | **192** |  | **194h** | 42[c] |

[a] All dr >19:1 unless otherwise stated. dr determined by $^1$H NMR analysis of the unpurified reaction mixtures. dr = (major isomer):Σ(other isomers). [b] dr 2:1. [c] dr 8:5.

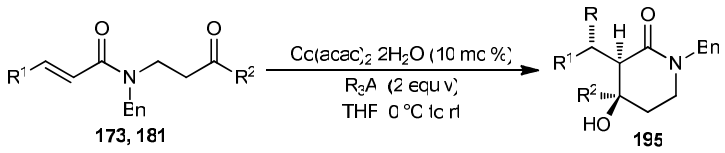
**Table 2.4**

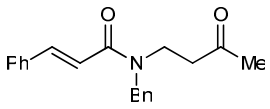
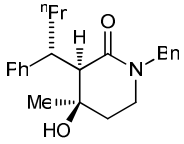
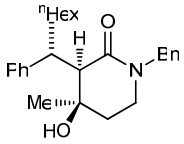
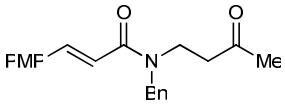
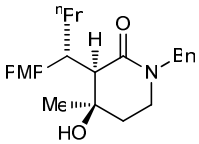
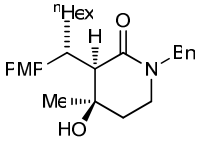
The cobalt-catalysed alkylative aldol cyclisations using $Me_3Al$ were less synthetically useful than those employing $Et_3Al$, as the products were generally obtained in lower yields. This observation was partly attributed to the lower reactivity of $Me_3Al$. In certain cases (entries 1, 2 and 5) full conversion of the starting material to the desired product was observed from the crude NMR spectra, which contained only minor impurities. For these examples, a full mass recovery was obtained after work-up and yet, following column chromatography, lower yields than those predicted were consistently observed. Unfortunately, attempts to improve these

yields *via* variation of chromatography solvents were not successful. As was observed with $Et_3Al$ (Table 2.3), variation of the aromatic substituents (entries 2-4) affected the transformation, with the more electron-donating groups favouring the alkylative aldol reaction. Replacing the pendant methyl ketone with either an ethyl group or an aromatic group had a detrimental effect on the diastereoselectivity of the reaction (entries 8 and 9).

### 2.2.5 Cobalt-Catalysed Alkylative Aldol Cyclisation Using Higher $R_3Al$

In order to probe the wider applications of this reaction, we attempted cyclisations employing higher trialkylalumiunium reagents. To our gratification, both tri-*n*-propyl- and tri-*n*-hexylaluminium proved to be suitable reagents for the reaction (Table 2.5).




| entry | substrate | | R | product | | yield[a] (%) |
|---|---|---|---|---|---|---|
| 1 |  | **173** | $^{n}$Pr |  | **195a** | 58 |
| 2 | | | $^{n}$Hex |  | **195b** | 75 |
| 3 |  | **181** | $^{n}$Pr |  | **195c** | 62 |
| 4 | | | $^{n}$Hex |  | **195d** | 61 |

[a] All dr >19:1. dr determined by $^{1}$H NMR analysis of the unpurified reaction mixtures. dr = (major isomer):Σ(other isomers).

**Table 2.5**

Substrates containing a phenyl-substituent (**173**, entries 1 and 2) and a *para*-methoxyphenyl-substituent (**181**, entries 3 and 4) at the β-position of the α,β-unsaturated amide both underwent the alkylative aldol cyclisation with $^{n}Pr_3Al$ and $^{n}Hex_3Al$. High levels of diastereoselectivity were maintained under these conditions and the products were isolated in good yield.

## 2.2.6 Substrate Scope

At this stage it became desirable to explore the scope of the reaction further by testing substrates whose structures were substantially different to those previously examined under our reaction conditions (Fig 2.1).

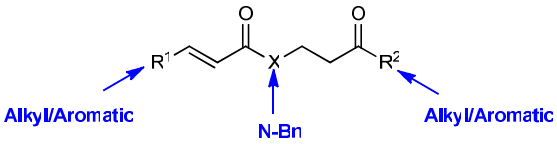
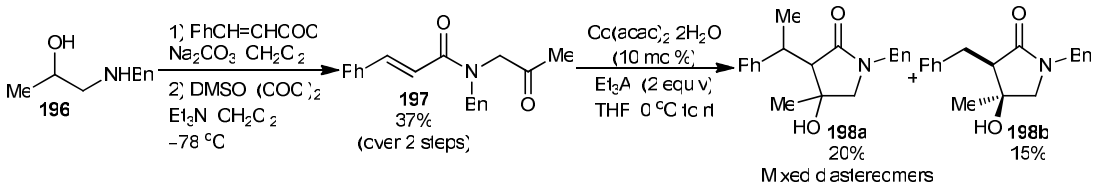



**Figure 2.1**

The general substrate structure contains a benzyl-protected amide as the tether, a ketone as the appendant electrophile and has the appropriate skeleton to result in the six-membered cyclic lactam products observed. The variations investigated included different skeletal arrangements, different types of tether and variation of the electrophilic trap, in the hope of accessing a more diverse range of cyclic products.

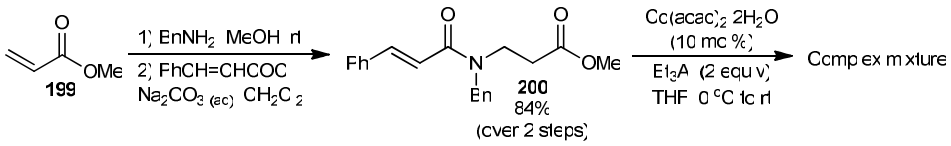
The first variation investigated was a substrate with one methylene group less in the carbon backbone, to provide a potential route into pyrrolidinones *via* our alkylative aldol approach. The amide substrate (**197**) was made *via* an alkylation reaction with a subsequent Swern oxidation (Scheme 2.8).




**Scheme 2.8**

Under our standard conditions, the reaction did not proceed to conversion and provided a complex mixture of products. It was not possible to isolate all of these products but 15% of the reductive aldol product was obtained along with 20% of what appeared to be a mixture of the alkylative aldol diastereomers.

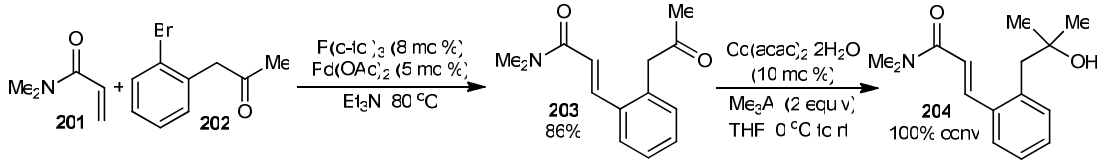
The electrophilic trap was next examined and a substrate possessing a pendant ester group was prepared. Alkylation of benzylamine with methyl acrylate and a subsequent acylation provided the desired substrate **200** in 84% yield over the two steps (Scheme 2.9).




**Scheme 2.9**

Application of our standard $Co(acac)_2$ and $Et_3Al$ conditions to **200** resulted in a complex mixture of products; containing no trace of any alkylative aldol cyclisation product (Scheme 2.9).

The next variation investigated involved a significant change to the core skeleton of the general structure; substrate **203**, containing an aromatic group in the backbone was synthesised *via* a Heck-type reaction from the aryl bromide **202** and the α,β-unsaturated amide **201** in good yield (Scheme 2.10)

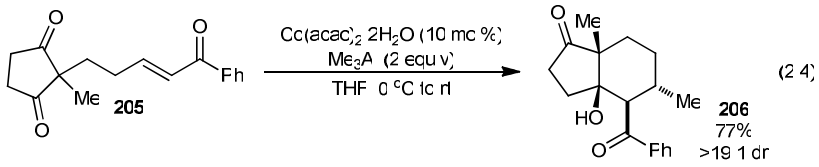



**Scheme 2.10**

Under our alkylative aldol conditions of $Co(acac)_2$ and $Me_3Al$, it appeared that direct addition to the appendant ketone had occurred, although the product **204** was never isolated.

Finally, a substrate[i] containing an α,β-unsaturated ketone as the initial Michael acceptor and a 1,3-dione as the electrophilic trap (**205**)[63] was subjected to our reaction conditions (eq 2.4).

[i] This substrate had been prepared according to the literature procedure by Katherine Watson.

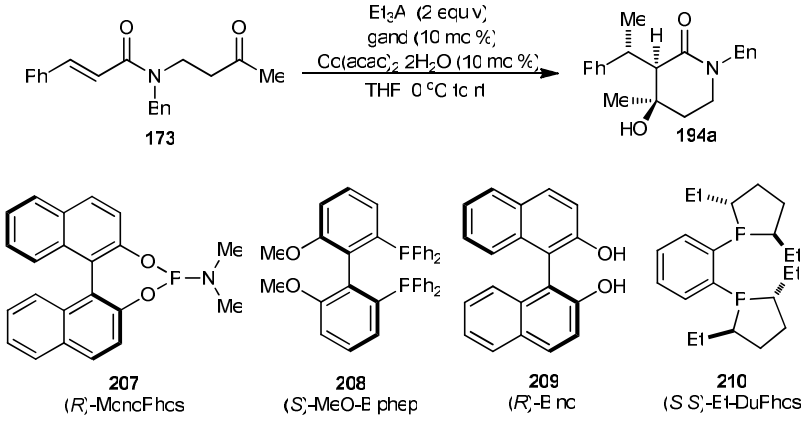



The conjugate addition–aldol reaction proceeded smoothly for the highly reactive precursor **205** and the desired bicyclic product **206** was isolated in a good yield with excellent diastereoselectivity. The relative stereochemistry of the product has been assumed based on similar transformations that have been reported by Krische and co-workers.[48]

### 2.2.7 Screening for Enantioselectivity

The synthetic utility of this reaction protocol would be powerfully enhanced if the conjugate addition step could be rendered enantioselective, since three new contiguous stereocentres could be created with absolute stereocontrol. Therefore a concerted effort was directed at screening different metal catalyst and ligand combinations to achieve this goal.

The substrate **173** was used as our model system in the alkylative aldol cyclisation using $Et_3Al$. In the initial examination, a range of the more commonly available chiral non-racemic ligands were screened in conjunction with $Co(acac)_2$ (representative examples are illustrated in Scheme 2.11).

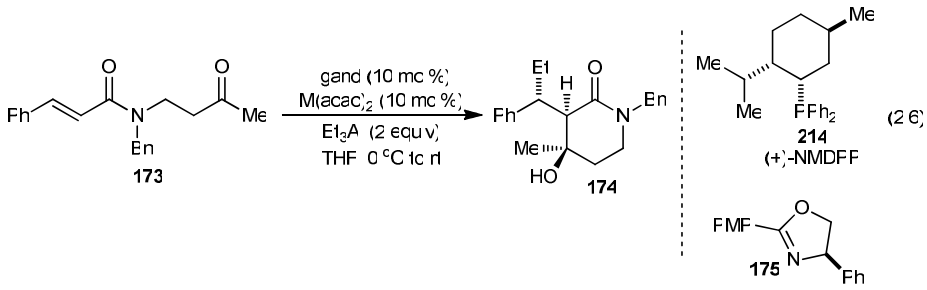


**Scheme 2.11**

Unfortunately none of these ligands offered any levels of asymmetric induction. Furthermore, the results indicated that bis-phosphines such as (*S*)-MeO-Biphep and (*S,S*)-Et-DuPhos appeared to suppress the catalytic activity.

It was postulated that perhaps more specialised ligands would be required to effect the desired transformation. The literature provided two possible ligand systems that we hoped would meet with greater success. The first was Ikeda's chiral monodentate oxazoline **175**, which was used during the optimisation studies (*vide supra*).[62] The second was the monophosphine ligand, (+)-NMDPP, that Jamison used in the reductive coupling of alkynes and aldehydes in the presence of $Ni(cod)_2$ and $Et_3B$ (eq 2.5).[64]

These two ligands were screened for enantioselectivity using both nickel and cobalt catalysts and $Et_3Al$ (eq 2.6).

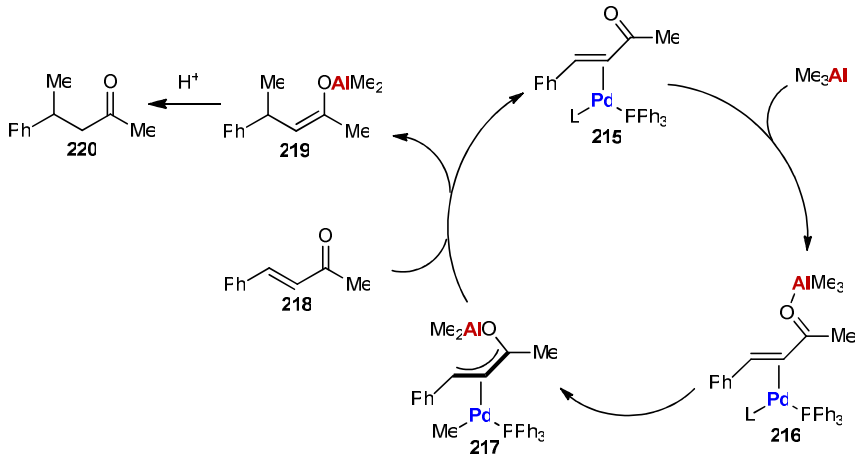



The combination of the $Co(acac)_2$ catalyst and $Et_3Al$ with both the oxazoline **175** and the (+)-NMDPP ligands did provide 100% conversion to the desired alkylative aldol product but no asymmetric induction was detected. Unfortunately the other conditions proved to be even less successful and the combination of the nickel catalyst and $Et_3Al$ resulted in the reductive cyclisation product **161a** in both cases.

At this stage, screening for asymmetric induction was suspended. Although the reasons for the lack of enantioselectivity were unclear, we postulated that these chiral non-racemic ligands were not coordinating sufficiently to the cobalt centre. It was also possible that the cobalt catalyst was not directly involved in the stereochemical determining step (i.e. the delivery of the ethyl group) but instead ethyl addition may have been occuring *via* a radical mechanism (*vide infra*).

### 2.2.8 Plausible Reaction Mechanism

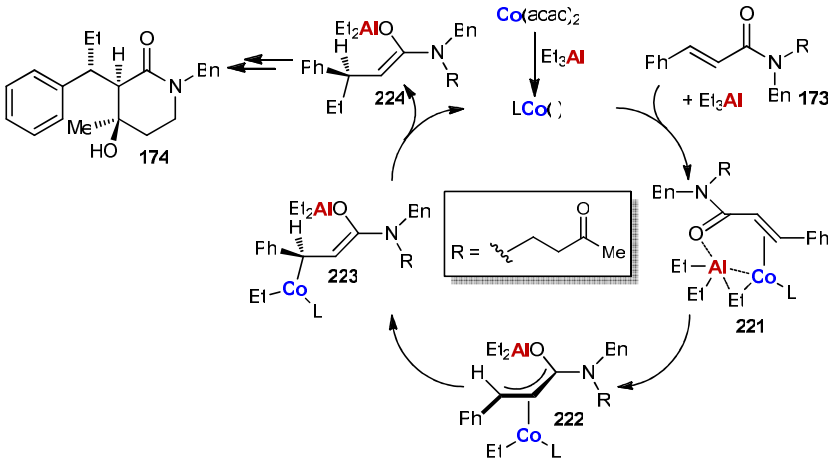
The generation of π-allylmetal species by Lewis acid-promoted oxidative addition of low-valent transition metals to α,β-unsaturated carbonyl compounds is well documented in the literature. For example, Mackenzie's group have described allylnickel reagents[65,66] and, more recently, Ogoshi and co-workers have published a number of papers on palladium π-allyl species.[67,68] During an investigation into the roles of Lewis acids in transition metal-catalysed conjugate additions, they used NMR studies to deduce that the treatment of $Pd(PhC{=}CHCOMe)(PPh_3)_2$ with $AlMe_3$ leads to a palladium complex containing $\eta^3$-allyl coordination. Based on this observation they suggest the following mechanism for the palladium catalysed conjugate addition of $Me_3Al$ to α,β-unsaturated ketones (Scheme 2.12).



**Scheme 2.12**

Initially, intermediate **216** is formed after coordination of $Me_3Al$ to the palladium-enone complex **215**. A subsequent oxidative addition and transmetallation give the key $\eta^3$-allyl(methyl)palladium intermediate **217**. Reductive elimination liberates the conjugate addition product **220** (after work-up) and coordination of further enone to the palladium centre completes the cycle.

Drawing from these precedents we suggest the participation of a π-allylcobalt species in our catalytic cycle. The proposed mechanism has been depicted using substrate **173** and $Et_3Al$ for illustrative purposes (Scheme 2.13).



**Scheme 2.13**

In the presence of $Et_3Al$ it is supposed that $Co(acac)_2$ is reduced *in situ* to a Co(I) species. In the presence of excess $Et_3Al$, Co(I) can coordinate to the α,β-unsaturated amide to give intermediate **221**, which contains a three-centre-two-electron bridging interaction between the cobalt, aluminium and ethyl ligand. Both Montgomery[69] and Ogoshi[70] have suggested this type of species previously (Fig 2.2).

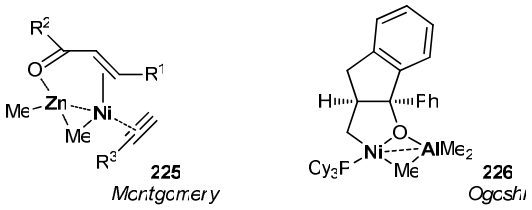
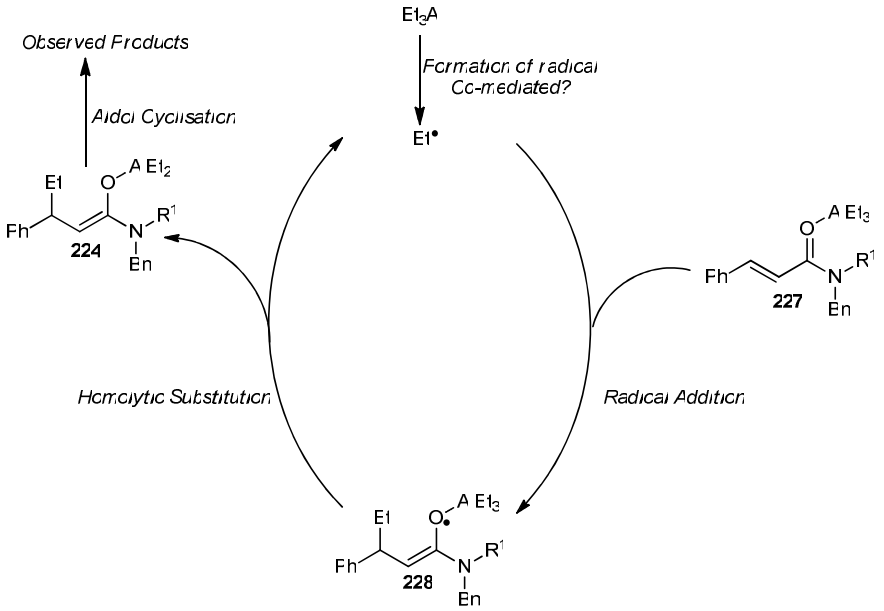



**Figure 2.2**

The group of Montgomery conducted a series of experimental and computational studies on the role of $Me_2Zn$ in the nickel-catalysed coupling of an enone and an alkyne. They concluded that the $Me_2Zn$ plays a dual Lewis basic/Lewis acidic role in these reactions; Lewis acidic activation of the carbonyl and Lewis basic activation of the Ni(0) species *via* a three-centre-two-electron bridging interaction of the Zn–Me bond with the nickel (**225**, Fig 2.2).[68] In addition, Ogoshi reported the crystal structure of **226**, containing a bridging methyl group.[69] In our case we have replaced the nickel with cobalt, and $Me_2Zn$ or $Me_3Al$ with $Et_3Al$, but the principle remains the same. Oxidative addition of Co(I) to the α,β-unsaturated amide, with subsequent transmetallation results in **222**, which undergoes a hapticity change from $\eta^1$ to $\eta^3$ to give **223**. At this stage reductive elimination provides the *Z*-aluminium enolate **224** and the active Co(I) catalyst is regenerated. It is supposed this species undergoes the diastereoselective aldol cyclisation to result in the β-hydroxylactam product upon work-up.

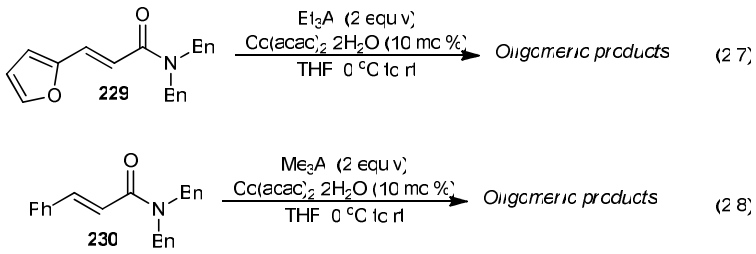
In light of the recent work carried out by Bertrand and co-workers on the dialkylzinc-mediated radical conjugate addition–aldol reactions (see Chapter 1), it is unwise to rule out a radical pathway when considering our mechanism (Scheme 2.14).




**Scheme 2.14**

In the presence of $Co(acac)_2$ or trace amounts of oxygen in the reaction vessel, it is possible that an ethyl radical is produced from $Et_3Al$. This species can then attack at the β-position of the Lewis acid-activated α,β-unsaturated amide to produce intermediate **228**. Drawing precedent from the dialkylzinc-mediated transformations, it is fair to assume that homolytic substitution can take place at aluminium and form the aluminium enolate **224** and regenerate the ethyl radical in the catalytic cycle. The aluminium enolate can then be supposed to cyclise as discussed previously. If a radical-mediated mechanism were indeed in operation this could account for the lack of asymmetric induction observed during the screening for enantioselectivity.

There is evidence to suggest that the situation is perhaps more complex than the scenarios outlined above. The cobalt-catalysed conjugate additions of $R_3Al$ to the simpler amide substrates **229** and **230** containing no tethered ketones were unsuccessful (eq 2.7 and eq 2.8). In both cases, it appeared that oligomerisation of the starting material had taken place and there was no evidence of any conjugate addition.




Furthermore, the decreased levels of diastereoselectivity observed in the case of the pendant phenyl ketone (entry 11, Table 2.3), which is accompanied by an increased proportion of the competitive conjugate reduction, implies that some participation or activating coordination of the pendant ketone cannot be ruled out.

### 2.2.9 Stereochemical Rationale

The relative stereochemistry of the major diasteromer of the β-hydroxylactam products was confirmed by X-ray crystallography of the products **174** and **193h** (Fig 2.3 and Fig 2.4). The relative stereochemistries of the remaining products were assigned by analogy.

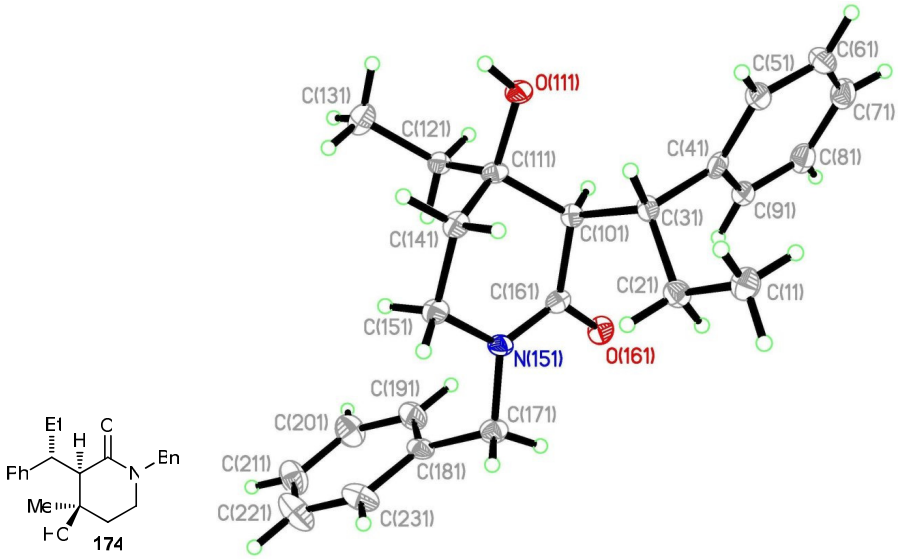



**Figure 2.3**

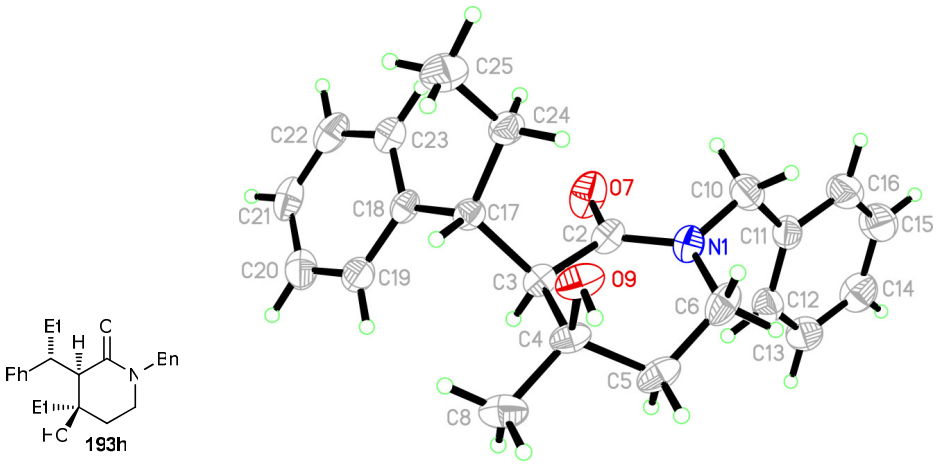
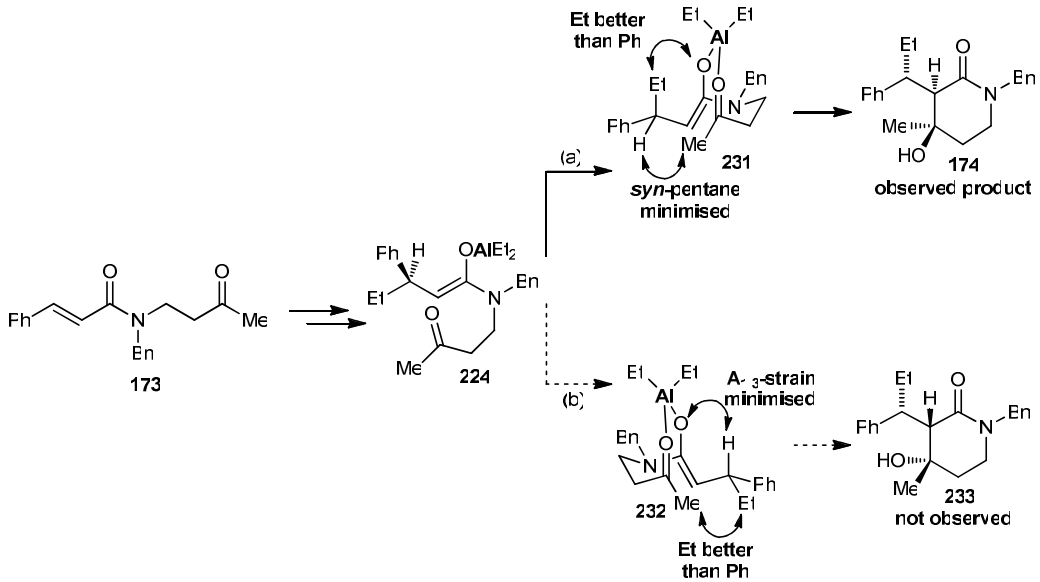



**Figure 2.4**

Initially, the exceptionally high levels of diastereoselectivity observed for the majority of substrates were slightly surprising, as the new stereogenic centre formed upon conjugate addition was outside of the six-membered ring formed upon cyclisation. If we assume that the aldol cyclisation of **173** occurs *via* a chelated Zimmerman-Traxler transition state[46] then two conformations appear reasonable (Scheme 2.15).




**Scheme 2.15**

In route (a), cyclisation through **231** minimises unfavourable *syn*-pentane interactions,[71] whereas in route (b) cyclisation through **232** minimises $A_{1,3}$-strain[72] in

the enolate. Based on these arguments it appears that minimisation of *syn*-pentane interactions dominates and so **174** is obtained as the sole product in the majority of cases.

Again, as discussed previously, the situation could be more complex if the coordination of the pendant ketone to the cobalt and/or aluminium centres occurs in any of the intermediates **221-223**, as this coordination would fix the ketone on one particular diastereotopic face of the aluminium enolate leading to important stereochemical consequences.

## 2.3 Conclusions

A novel cobalt-catalysed alkylative aldol cyclisation of α,β-unsaturated amides with a pendant ketone has been described, using a range of different trialkylaluminium reagents. It is significant that, prior to our work, there were no literature reports of metal-catalysed conjugate addition of trialkylaluminium reagents to α,β-unsaturated amides. The reaction generally proceeds with high levels of diastereoselection and provides β-hydroxylactam products in good yields. Attempts to further expand the substrate scope have been discussed and the use of chiral non-racemic ligands has not imparted any enantioselectivity to the reaction, although the reasons for this have not yet been elucidated. Various mechanistic pathways have been postulated including one involving a π-allylcobalt species and the other comprising of a radical-mediated pathway. A stereochemical rationale has been proposed to account for the high diastereoselectivity of the reaction, which suggests *syn*-pentane strain is the dominant stereocontrol element.

# 3.0 The Chemistry of Enamides

## 3.1 Introduction

The synthetic community has utilised silyl enol ethers as effective intermediates in a wide range of transformations for many decades.[73] Despite their widespread popularity, they often have to be directly prepared before use as they are relatively unstable, being prone to hydrolysis and protonolysis. Additionally, the stereoselective synthesis of more highly substituted silyl enol ethers is often non-trivial.[73a] The closely related enamines are also recognised as useful enolate equivalents and play significant roles in asymmetric organocatalytic reactions.[74] Enamines are more highly reactive than silyl enol ethers but suffer a low stability due to their propensity to hydrolyse. Enamides offer a potential solution to this problem, as they possess a degree of nucleophilicity due to their enaminic character, yet the presence of an electron-withdrawing group on the nitrogen tempers this reactivity and increases the stability of the enamide.[75] This feature allows them to be purified by column chromatography and stored for long periods of time. Therefore, enamides are valuable intermediates to a synthetic chemist (Fig 3.1).

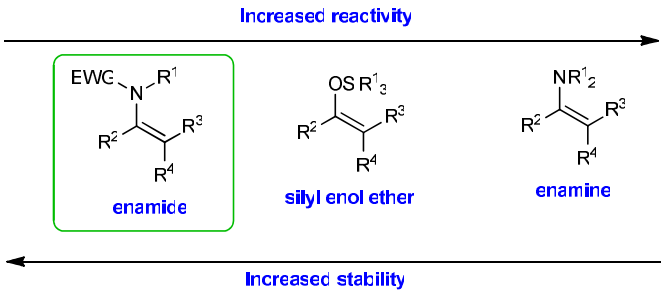



**Figure 3.1**

In addition to its importance as a synthetic intermediate, the enamide functionality is present in several biologically active natural products such as TMC-95A-D,[76] croacins A, B and D[77] and the salicylihalamides and related compounds.[78] Consequently there has been a significant volume of work undertaken to investigate

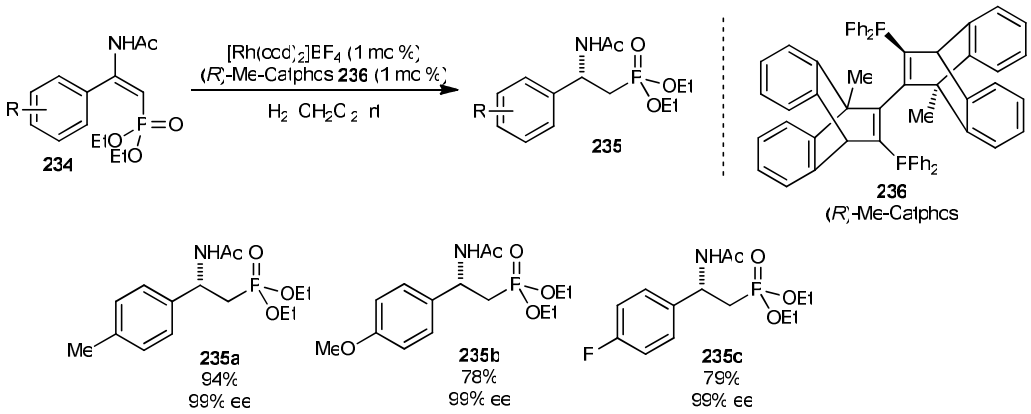
the chemistry of enamides and their synthesis in a stereo- and regiocontrolled manner.

## 3.2 Applications of Enamides

Enamides, as synthetic intermediates, offer a diverse range of chemistry; they are able to act as both nucleophiles and electrophiles and participate in pericyclic, radical and transition metal-catalysed reactions. They can also be applied in the synthesis of heterocycles and the preparation of optically active amines and amino acid derivatives. Recent reviews by Carbery[79] and Kobayahsi[80] have covered most of these topics in some detail and the work is too wide-ranging to cover it comprehensively within the remits of this discussion. Thus we will examine the key areas, highlighting recent examples to appreciate the depth and breadth of enamide applications across organic synthesis.

### 3.2.1 Asymmetric Hydrogenation of Enamides

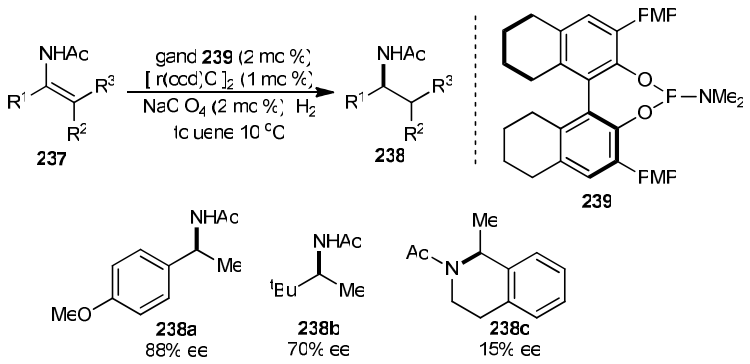
The preparation of optically active amines and their derivatives is arguably the best-known application of enamides. Extensive research has been undertaken on the rhodium catalyst, in conjunction with both chelating and monodentate phosphine ligands.[81] Recently, Doherty and Knight described a Rh-(*R*)-Me-Catphos complex as an effective catalyst for the asymmetric hydrogenation of (*E*)-β-aryl-β-enamidophosphonates (Scheme 3.1).[82] The β-amidophosphonates products **235** can act as precursors to β-aminophosphonic acids, which are substrates that exhibit antibacterial and antifungal activity.



**Scheme 3.1**

Furthermore, the group discovered a complementary Rh-(*R*)-(*S*)-Josiphos catalyst for the reaction of (*Z*)-enamides.[82] In both cases, exceptionally high conversions and levels of asymmetric induction were observed.

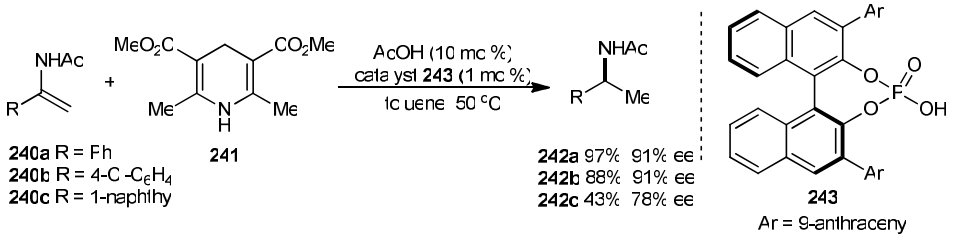
It is possible to utilise other transition metals as catalytic species in the asymmetric hydrogenation reaction. For example, Beller and co-workers demonstrated the use of an iridium catalyst in the presence of 3,3'-substituted H8-phosphoramidites (Scheme 3.2).[83]



**Scheme 3.2**

Employing $NaClO_4$ as an additive was found to increase the enantioselectivity of the reaction. Since iridium species can form active dimeric complexes, it was surmised that the addition of this non-coordinating anion stabilises the more selective monomeric iridium catalyst.

In addition, there have been reports of non-metal-catalysed hydrogenation reactions involving enamides. In the last year, Antilla has devised a dual chiral–achiral acid-catalysed enantioselective reduction of enamides, using the Hantzsch ester[84] as the hydride source (Scheme 3.3).[85]




240a R = Ph
240b R = 4-C -C$_6$H$_4$
240c R = 1-naphthy

241

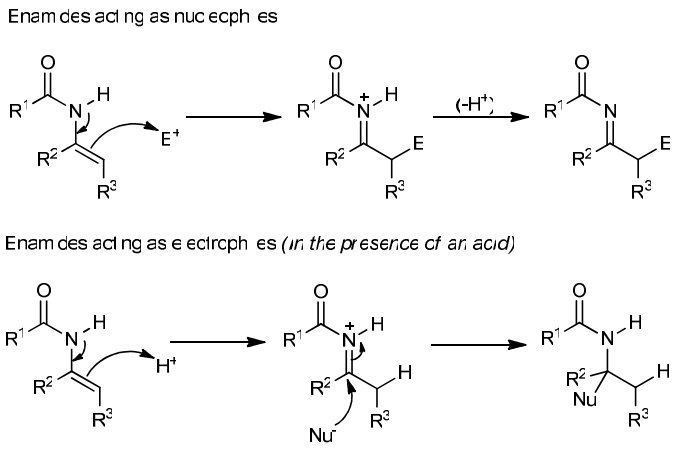
242a 97% 91% ee
242b 88% 91% ee
242c 43% 78% ee

**Scheme 3.3**

In the absence of the achiral acid additive, the reaction rate was intolerably slow at lower catalyst loadings and this was attributed to the slow formation of the iminium ion. Acetic acid was employed to facilitate iminium ion formation whilst being inactive in the hydrogenation step, thus the high levels of enantioselectivity were maintained.

### 3.2.2 The Enaminic Character of Enamides

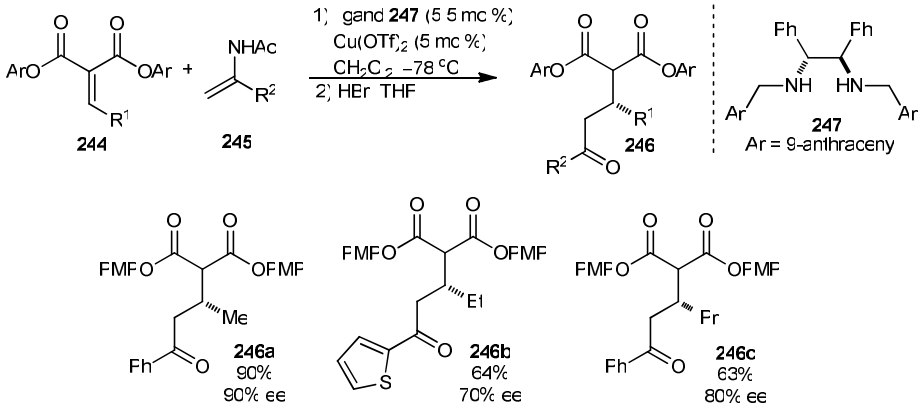
Despite the electron-withdrawing group attached to the nitrogen, enamides possess a degree of enaminic character and so are able to act as nucleophiles. Additionally, this trait allows them to form iminium ions in the presence of acid and thus they can also act as electrophilic species under the appropriate conditions (Scheme 3.4).




**Scheme 3.4**

Consequently, enamides have been successfully exploited as both electrophilic and nucleophilic reagents by a number of groups in recent years.

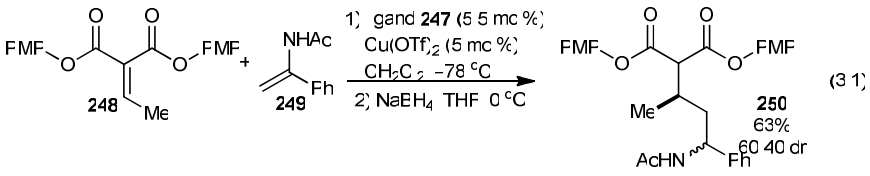
Kobayashi pioneered the use of enamides as nucleophiles in a number of enantioselective reactions with various electrophiles such as iminophosphonates,[86] ethyl glyoxyate[87] and azodicarboxylates[88] under copper catalysis. One of the latest examples to emerge from their laboratories has been the copper-catalysed asymmetric conjugate addition of enamides to alkylidenemalonates (Scheme 3.5).[89]



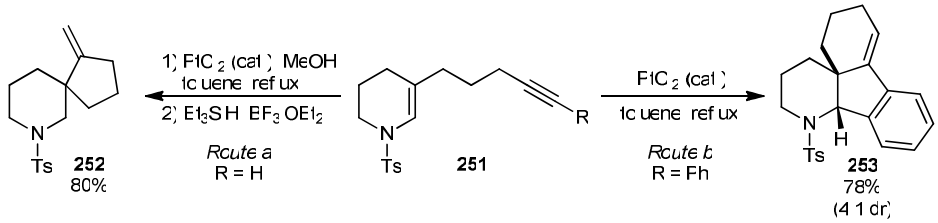

**Scheme 3.5**

The initial adducts formed in the Michael reaction are imines and in the majority of cases they were hydrolysed to form the corresponding ketones. However, the use of

$NaBH_4$ provided an effective route to amino ester products albeit with modest diastereoselectivity (eq 3.1).



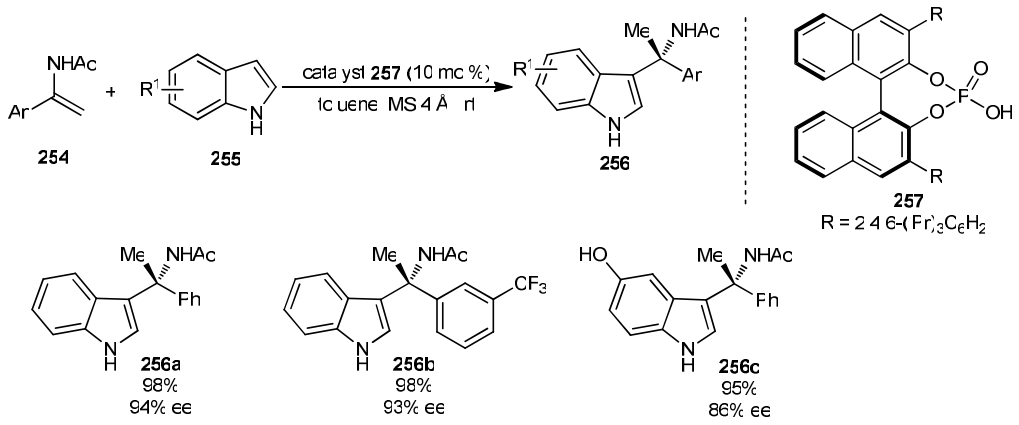

Dake and co-workers demonstrated the use of enamides as nucleophiles in platinum-catalysed spirocyclisation reactions onto a tethered alkyne (Route a, Scheme 3.6).[90]




**Scheme 3.6**

This methodology allowed easy access to spiro-piperidine structures. However, when the tethered alkyne was substituted with an aromatic group an alternative pathway resulted in the tetracyclic product **253** (Route b, Scheme 3.6).[90b] In this instance, nucleophilic attack of the enamide on the Pt(II)-activated alkyne is followed by a Friedel–Crafts ring closure. This methodology has been employed by Zhai and co-workers as a route to the tetracyclic core found in the natural product nakadomarin.[91]

As demonstrated in the previous Friedel–Crafts ring closure (Route b, Scheme 3.6), in the presence of acid, enamides can be converted into their iminium ion counterparts. These electrophilic species can participate in other types of Friedel–Crafts reactions. For example, Zhou described a chiral Brønsted acid-catalysed Friedel–Crafts reaction of indoles with α-aryl enamides (Scheme 3.7).[92]

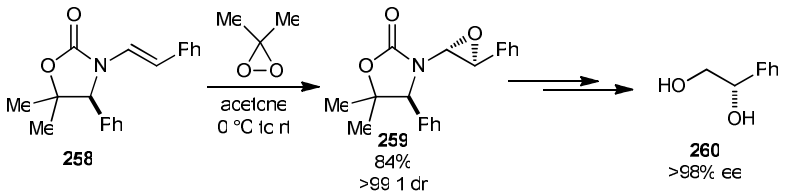



**Scheme 3.7**

The transformation elegantly allows the assembly of enantioenriched indoles, which contain a nitrogen-bearing quaternary stereocentre.

### 3.2.3 Chiral Enamides in Stereoselective Synthesis

The preparation of chiral enamides is relatively facile and these substrates can function effectively as inducers of enantioselectivity in a number of transformations. For example, Davies and co-workers recently devised a route to homochiral 1,2-diols from both (*E*)- and (*Z*)-enamides (Scheme 3.8).[93]

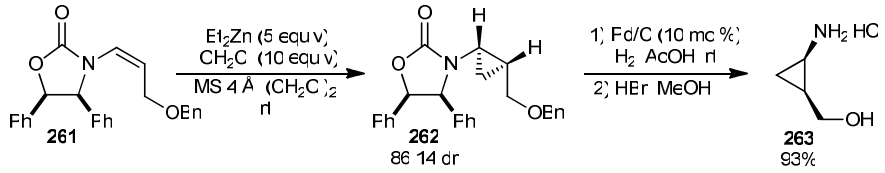



**Scheme 3.8**

The highly diastereoselective epoxidation using dimethyldioxirane is followed with a ring opening using *m*CPBA and a subsequent reductive cleavage provides the desired 1,2-diols with high levels of enantioselectivity.

Hsung has also undertaken work on the epoxidation of enamides, subsequent investigations by his group have focused on the cyclopropanation reaction of

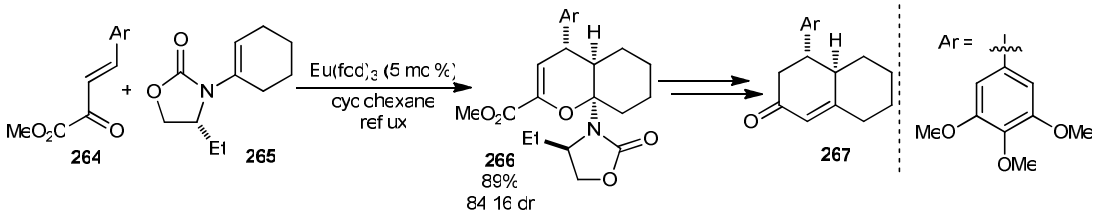
enamides. In recent years, they have reported the Simmons–Smith cyclopropanation of enamides as being highly stereoselective for a variety of enantiopure (*E*)- and (*Z*)-enamides (Scheme 3.9).[94]




**Scheme 3.9**

The enantiopure aminocyclopropane **263** is accessible *via* the removal of the chiral amide moiety from the major diastereomeric product **262** of the Simmons–Smith cyclopropanation. Hsung has also lately described an additional stereoselective cyclopropanation of enamides which utilises rhodium carbenoid species.[95]

An additional example of chiral enamides inducing enantioselectivity is a hetero-Diels–Alder reaction of enamides with oxadienes in the presence of $Eu(fod)_3$ (Scheme 3.10).[96]

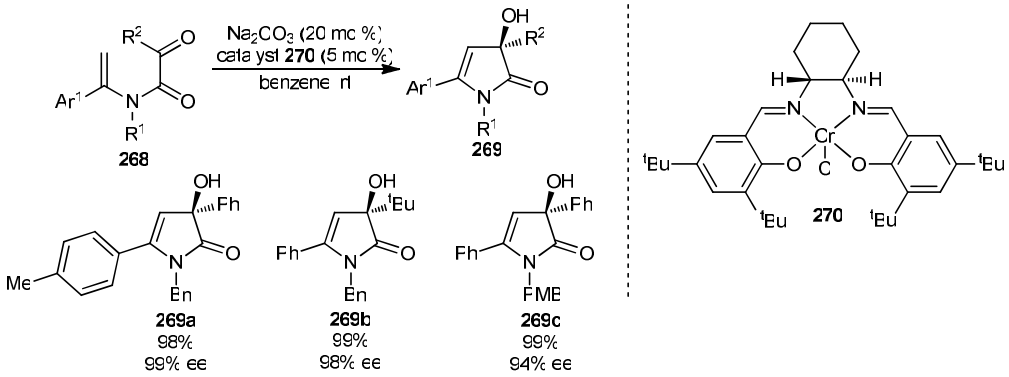



**Scheme 3.10**

The resultant bicyclic heteroadducts offer an asymmetric approach to 4-aryl-substituted octalones, *via* a series of transformations and removal of the oxazolidinone group.

### 3.2.4 Enamides in Heterocycle Synthesis

Enamides have been employed in the synthesis of a multitude of heterocycles including pyridines,[97] oxazoles,[98] indoles and indolines.[99] Wang and colleagues have recently devised a mild enantioselective synthesis of γ-lactams from enamides (Scheme 3.11).[100]



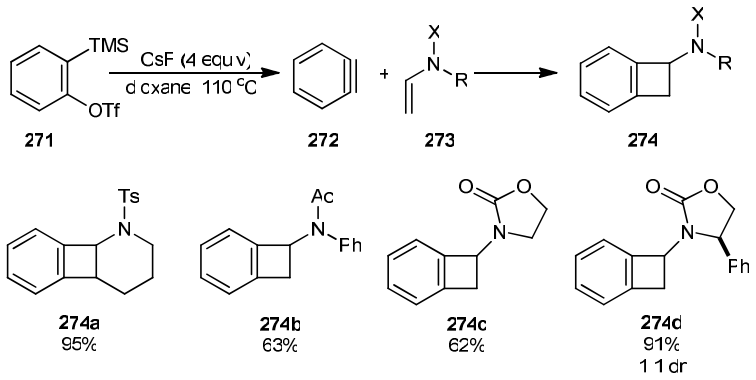

**Scheme 3.11**

This work allows the preparation of 1H-pyrrol-2(3H)-one derivatives containing a hydroxy-bearing quaternary stereocentre with high levels of enantioselectivity. The reaction additionally constitutes the first example of an asymmetric nucleophilic addition of a *tertiary* enamide to a carbonyl compound.

### 3.2.5 Pericyclic Reactions

Enamides are successful participants in a range of pericyclic transformations including sigmatropic rearrangements (e.g. an Ireland–Claisen rearrangement[101]) and cycloadditions (e.g. a [2+2] cycloaddition[102] and a hetero-Diels–Alder reaction[96]).

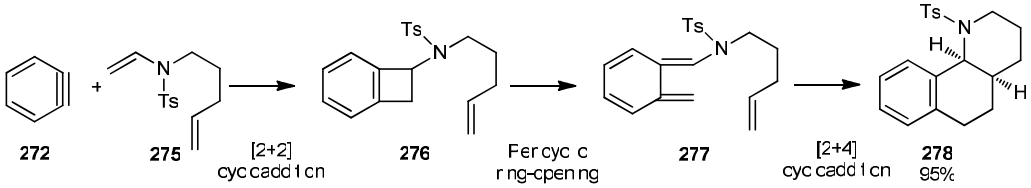
Hsung recently reported an enamide–benzyne [2+2] cycloaddition to construct amidocyclobutanes (Scheme 3.12).[102]




**Scheme 3.12**

A range of ynamide substrates underwent the [2+2] cycloaddition reaction, including yne-sulfonamides and those containing an oxazolidinone moiety.

Moreover, further investigations revealed that a tandem process was possible when using a tethered olefin (Scheme 3.13).




**Scheme 3.13**

The reaction involves a [2+2] cycloaddition, pericyclic ring opening and a subsequent [4+2] cycloaddition to give the *aza*-tricyclic product **278**. This methodology provides a rapid route to construct *N*-containing polycyclic structures.

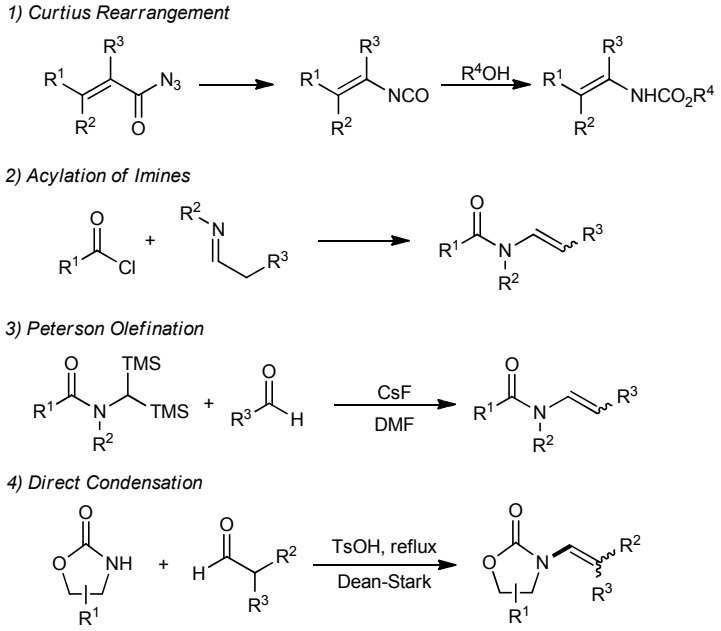
### 3.2.6 Conclusions

As synthetic intermediates, enamides are clearly valuable substrates willing to participate in a wide range of reactions. In addition to those mentioned (*vide supra*), enamides are able to take part in transition metal-catalysed reactions such as metathesis[103] and Heck reactions,[104] as well as radical[105] and photochemical[106] transformations. The chemistry of enamides and their derivatives continues to

flourish as their uses in organic synthesis are further explored. Thus the preparation of enamides is a vitally important topic.

## 3.3 Preparation of Enamides

Traditional methods of preparing enamides include the Curtius rearrangement of α,β-unsaturated acyl azides followed by reaction with an alcohol,[107] the acylation of imines,[108] the olefination of aldehydes[109] and the direct condensation of carbonyl compounds with amides or carbamates[110] (Scheme 3.14).




**Scheme 3.14**

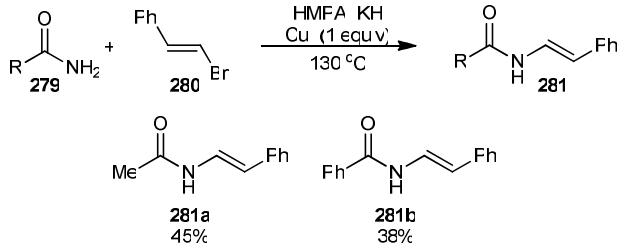
The Curtius reaction, imine acylation and amide olefination entail multiple steps in the preparation of starting materials and the yields of the desired enamides are often low. Moreover, the condensation method requires high temperatures and harsh conditions, which often resulted in unwieldy mixtures of regio- and stereoisomers. For the purposes of the proposed project, we will examine the latest advances in the regio- and stereocontrolled preparation of enamides.

### 3.3.1 Transition Metal-Catalysed Cross-Coupling

Recent innovations in transition metal-catalysed cross-coupling technologies have naturally meant that a great deal of attention has been focused on the *N*-alkenylation of amides with vinyl halides or sulfonates as an effective strategy to form enamides.[111]

#### *Copper-Catalysed Cross-Coupling*

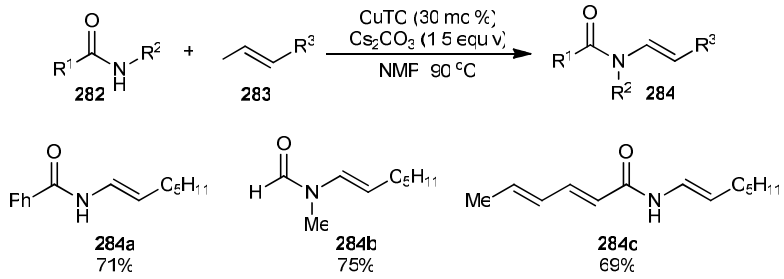
In 1991, Ogawa described the first copper-promoted direct vinylic substitution of a vinyl bromide with amides (Scheme 3.15).[112]




**Scheme 3.15**

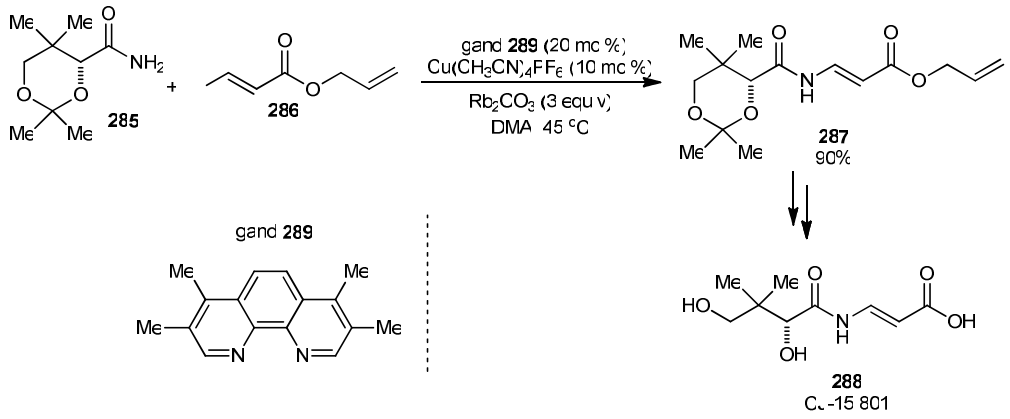
Stoichiometric amounts of copper and high temperatures gave the desired enamides with a high degree of stereoisomeric purity, although the observed yields were low.

Nearly a decade had elapsed before this methodology was rendered catalytic by the Porco group.[113] The use of copper (I) thiophenecarboxylate (CuTC) in conjunction with a polar, aprotic solvent and a carbonate base led to higher yields of the enamide products (Scheme 3.16).




**Scheme 3.16**

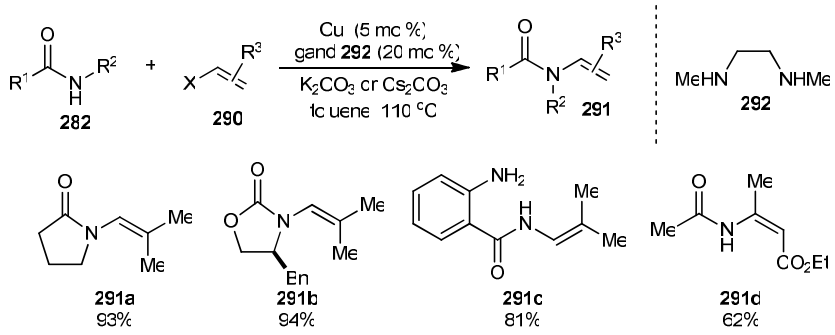
These catalytic conditions were applied directly to the synthesis of *O*-methyloxime enamide side chains, moieties present in salicylate antitumour macrolides. Extension of this protocol to the coupling of β-iodoacrylates was made possible by the use of rubidium carbonate as base and a modified phenanthroline ligand **289** (Scheme 3.17).[114]




**Scheme 3.17**

The robust nature of this methodology was demonstrated in the total synthesis of the antibiotic CJ-15,801 (**288**, Scheme 3.17). The key cross-coupling step between the amide **285** and the β-iodoacrylate **286** to give the intermediate **287** was achieved in an exceptionally high yield as one stereoisomer.

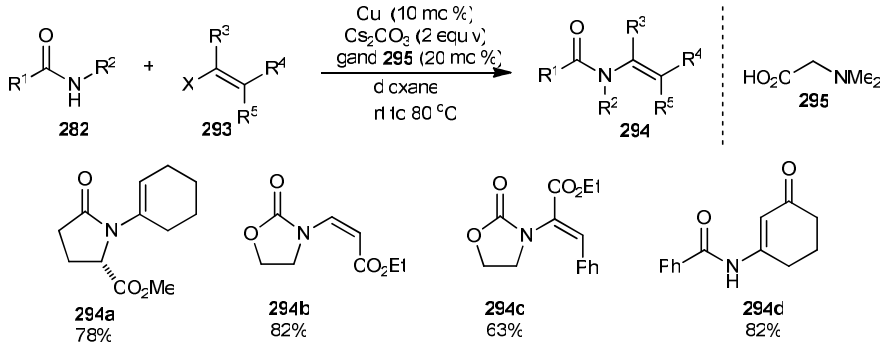
In 2003, Buchwald reported a more general procedure for the copper-catalysed cross-coupling synthesis of enamides, which was also effective for internal vinyl halides (Scheme 3.18).[115]




**Scheme 3.18**

Both vinyl bromides and vinyl iodides could be coupled with amides and carbamates in the high-yielding reaction. The mild conditions tolerated a range of functionalities and preserved the double bond geometry of the initial vinyl halides.

Shortly afterwards, Ma and co-workers reported similar results in the presence of *N,N*-dimethylglycine (Scheme 3.19).[116]




**Scheme 3.19**

Buchwald's group had found this ligand to be ineffective in toluene but in dioxane *N,N*-dimethylglycine was an efficient promoter of the coupling reaction. Moreover, under these conditions it was possible for the cross-coupling of some substrates to take place at room temperature.

The work of Porco, Buchwald and Ma stimulated a flurry of publications that described the copper-catalysed cross-coupling approach to obtain a number of

enamide-containing natural products[117] including oximidines I and III,[118] apicularen A,[119] various chartellines[120] and some clausena alkaloids[121] (Fig 3.2).

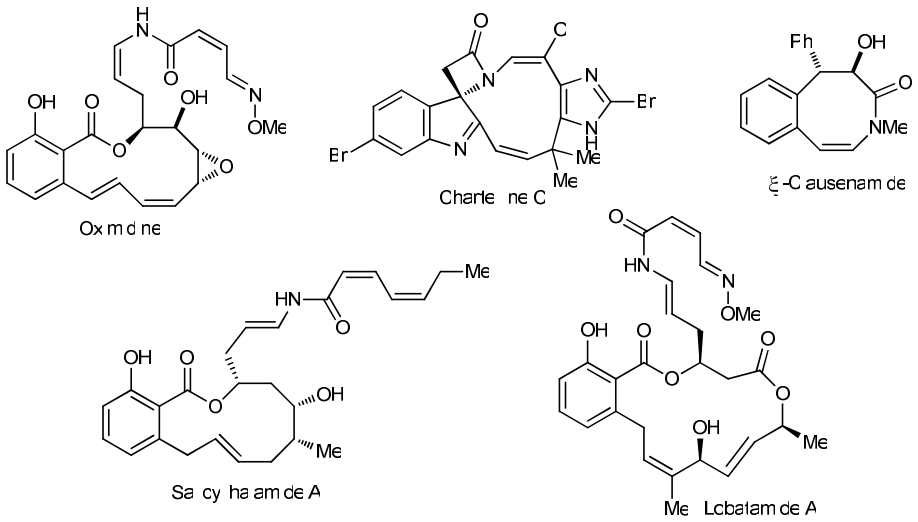
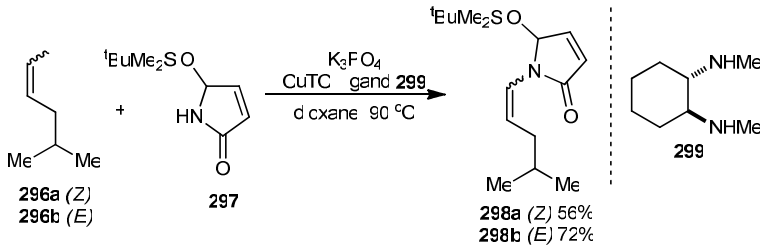



**Figure 3.2**

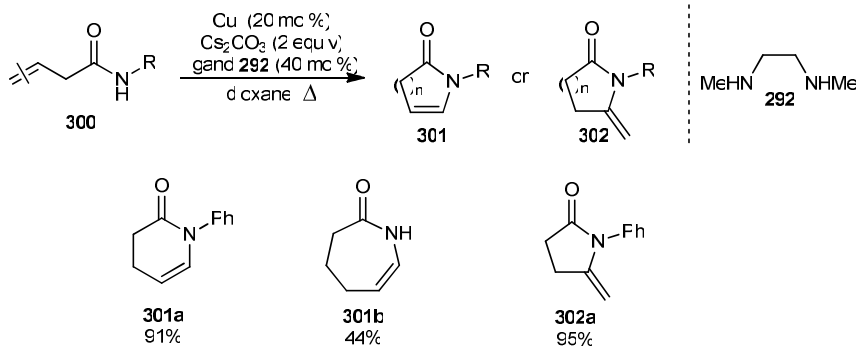
In an attempt to unify these strategies in a general procedure, Coleman and Liu reported the coupling of a *Z*- and an *E*-vinyl iodide with a protected maleimide hemiaminal to give the synthons **298a** and **298b** respectively (Scheme 3.20).[122]




**Scheme 3.20**

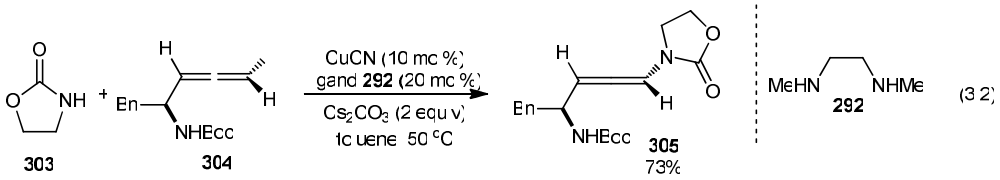
The substrates **298a** and **298b** can act as universal starting materials to the (*E*)- and (*Z*)-enamide side chains of a range of biologically active compounds including oximidines I, II and III, salicylihalamides A and B, lobatamides A and D and CJ-12,950.

Additional examples of this type include an intramolecular vinylation of amides to prepare five to seven membered ring lactams (Scheme 3.21).[123]



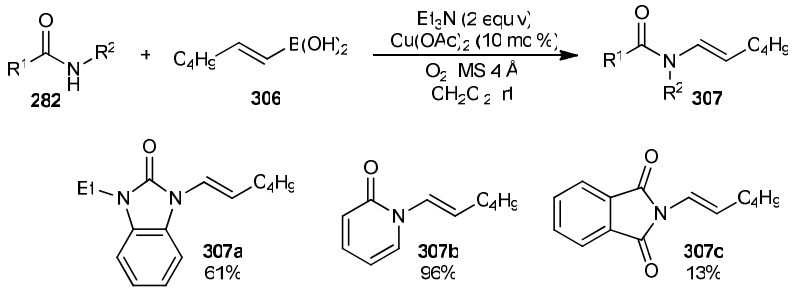

**Scheme 3.21**

It has also been possible to prepare optically enriched chiral allenamides *via* the stereospecific amidation of optically enriched allenyl iodides (eq 3.2).[124]



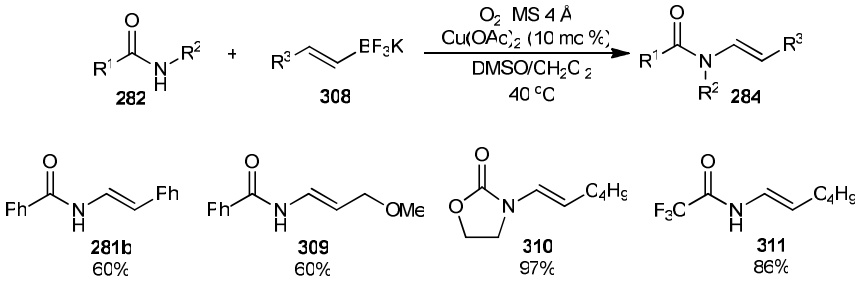

The reactions were carried out at a lower temperature due to the low thermal stability of the allenamides. The diastereomeric allenyl iodide **304** was coupled to the carbamate **303** with maintenance of the axial stereochemistry, indicating the stereospecificity of the transformation. At present the synthetic utility of this reaction is limited by the arduous preparation of optically enriched chiral allenyl iodides.

Lam and co-workers extended the scope of the copper-catalysed *N*-alkenylation of amides to include vinyl boronic acid coupling partners (Scheme 3.22).[125] In their report they described a procedure to oxidatively couple both N–H and O–H substrates to alkenylboronic acids in the presence of a catalytic amount of copper.



**Scheme 3.22**

Although lacking in generality (only three examples of amide-like substrates were coupled with the same alkenyl boronic acid) the reaction conditions were extremely mild. Replacement of the boronic acid with a potassium alkenyltrifluoroborate salt also gives the desired enamide coupling product (Scheme 3.23).[126]

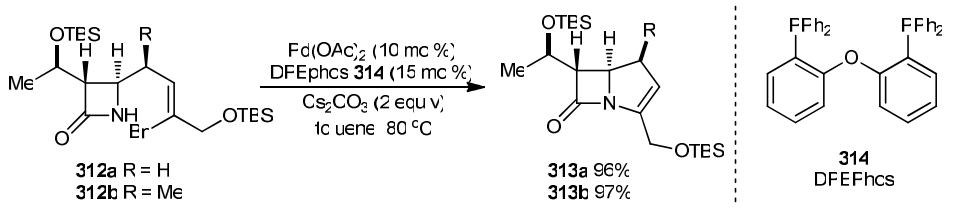


**Scheme 3.23**

This modification greatly improved the scope of the reaction and it was possible to couple primary amides and cyclic oxazolidinones to a variety of organotrifluoroborate salts.

### *Palladium-Catalysed Cross-Coupling*

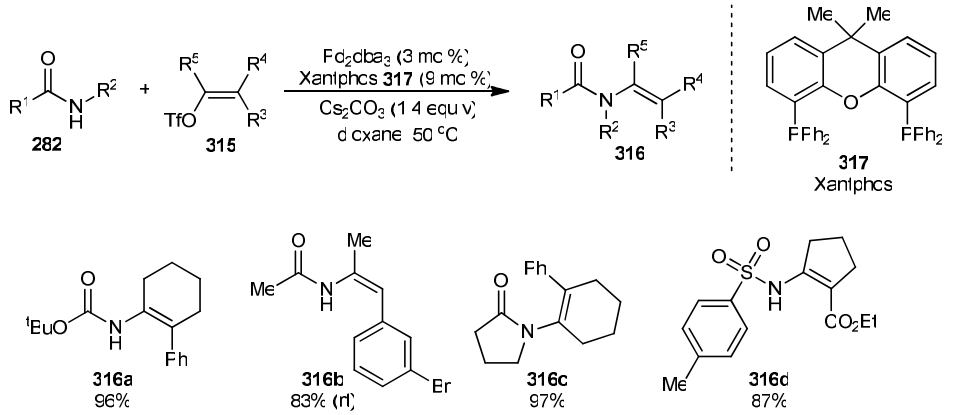
The majority of metal-catalysed cross-coupling reactions to form enamides are based on copper but a small number of palladium-catalysed protocols are also in existence. Mori made the first report of one such reaction in an intramolecular coupling to form β-lactams (Scheme 3.24).[127]




**Scheme 3.24**

The intramolecular coupling of a vinyl bromide with an amide resulted in a high conversion into a carbapenem skeleton for a small number of examples.

Researchers at Merck developed a more universal procedure for the palladium-catalysed cross-coupling of enol triflates with amides, carbamates and sulfonamides that takes place under extremely mild conditions (Scheme 3.25).[128]

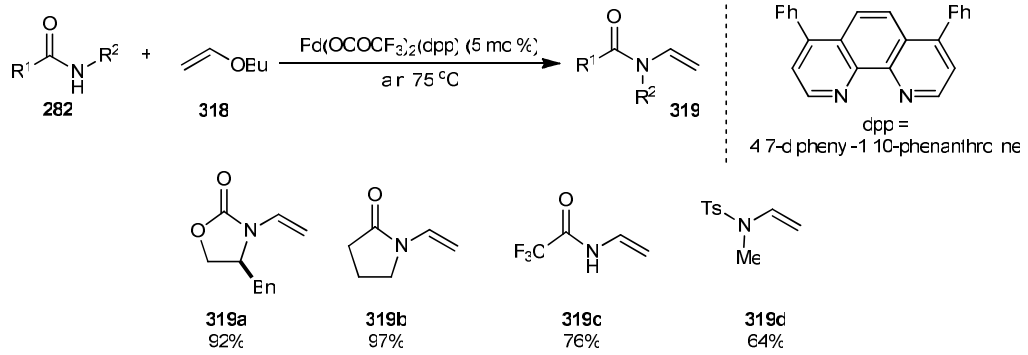



**Scheme 3.25**

At elevated temperatures isomerisation of the double bond geometry was observed for those substrates where isomerisation was possible. Therefore these examples were carried out at room temperature to obtain products of high stereoisomeric purity (**316b**, Scheme 3.25). Pleasingly the presence of a bromide in the coupling partner did not interfere with the desired transformation, highlighting the potential of this strategy in a multi-step synthesis. An advantage of employing enol triflates as coupling partners is that their stereoselective preparation is more facile than for their vinyl halide analogues. The construction of a single enol triflate from a ketone relies on simple kinetic versus thermodynamic control in the enolate formation step and

can be controlled by the appropriate choice of base and solvent. In a later paper the same group also reported the use of enol tosylates as coupling agents under slightly modified conditions.[129]

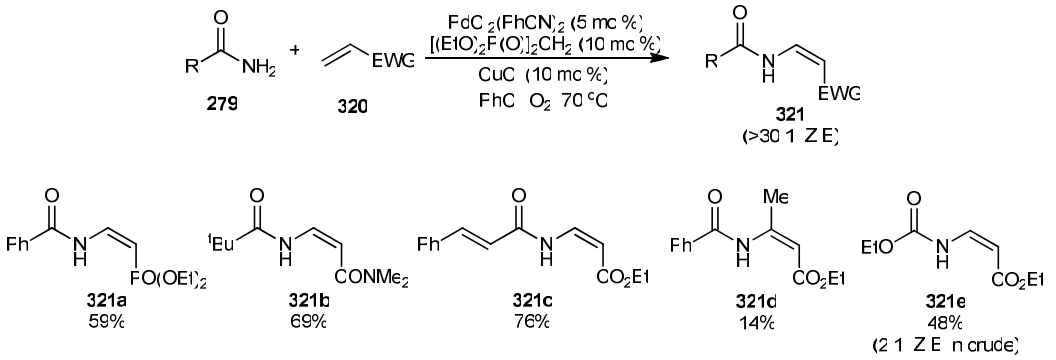
Stahl and co-workers published a novel formation of enamides *via* the palladium-catalysed vinyl transfer from vinyl ethers (Scheme 3.26).[130]




**Scheme 3.26**

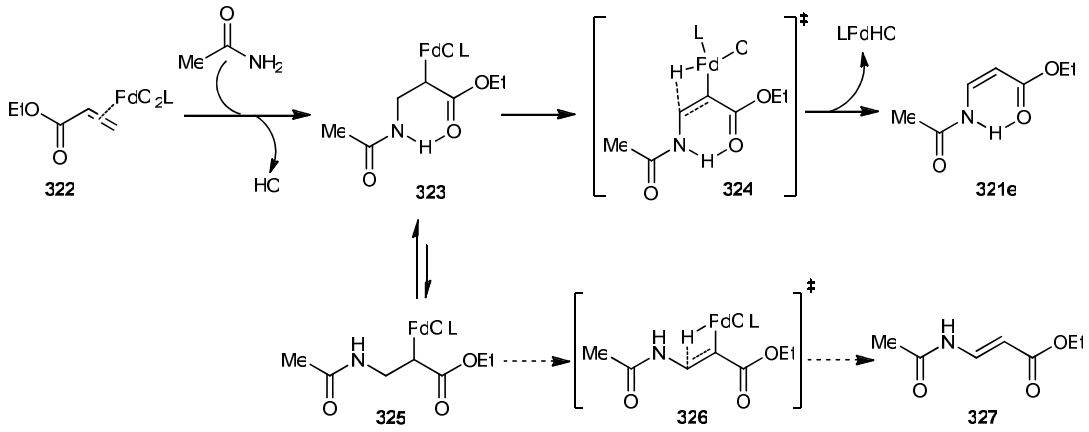
The formal cross-coupling reaction was successful with oxazolidinones, pyrrolidinones, primary amides and sulfonamides. The vinyl ether substrate was used in vast excess as the solvent in the reaction. No other vinyl ethers were subjected to the reaction conditions and so the methodology was restricted to the assembly of non-substituted enamides.

The palladium-catalysed coupling reaction was further developed to include a hydrogen bond-directed oxidative amidation of conjugated olefins (Scheme 3.27).[131] A variety of primary amides were reacted with acrylic esters, amides, alkyl vinyl ketones and vinyl phosphonates.



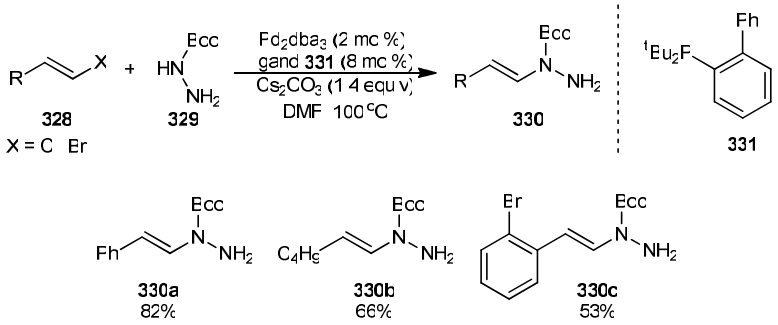

**Scheme 3.27**

Tetramethylenediphosphonate notably increased the reaction rates for the Pd/Cu cocatalytic system, as it suppressed the formation of palladium black. An additional benefit of this additive was that it inhibited the formation of an unwanted side product. The preferential formation of the *Z*-enamide was attributed to an intramolecular hydrogen bond between the amido N–H and the carbonyl group (Scheme 3.28). In the stereochemical-determining reductive elimination step the energy level of the transition state leading to the *Z*-enamide (**324**) was calculated to be significantly lower than that leading to the *E*-enamide (**326**), due to this intramolecular hydrogen bond. This finding may account for the lower selectivity observed when carbamates were employed as the N–H coupling partner; the lower acidity of the N–H proton would form a weaker intramolecular hydrogen bond.




**Scheme 3.28**

Another class of enamide-like compounds accessible *via* the palladium-catalysed cross-coupling strategy is the *N*-Boc-*N*-alkenylhydrazines (Scheme 3.29).[132]



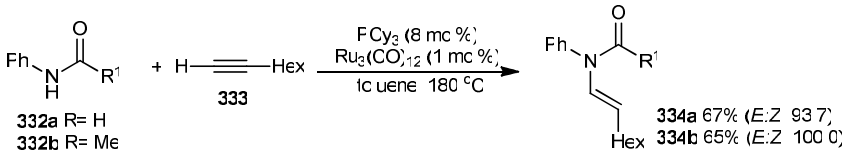

**Scheme 3.29**

The palladium-catalysed coupling of *tert*-butyl carbazate with a range of vinyl halides proceeds regioselectively through the *N*-Boc nitrogen to furnish an array of *N*-alkenylhydrazines in good yield.

The metal-catalysed cross-coupling approach has proven to be an effective way of accessing enamides stereoselectively. In particular, the robust nature of the copper-catalysed methodology has been demonstrated in its relatively widespread use in natural product syntheses over the last decade. However, the preparation of the requisite vinyl halide coupling partners is often non-trivial and imposes limitations on the synthesis of more highly substituted enamides.

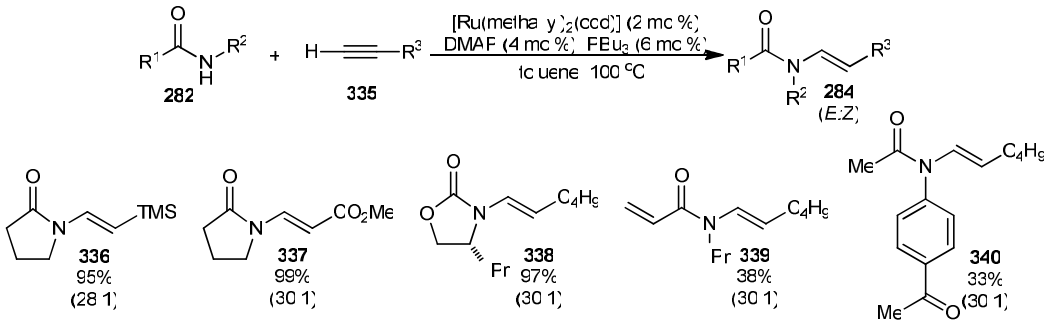
### 3.3.2 Hydroamidation of Terminal Alkynes

Enamides can be accessed *via* the addition of an N–H bond across an alkyne; Kondo and co-workers described the earliest catalytic example of one such reaction. The ruthenium-catalysed hydroamidation of an unactivated alkyne took place under high temperature and pressure conditions to yield a narrow range of *N*-aryl substituted *E*-enamides (Scheme 3.30).[133]



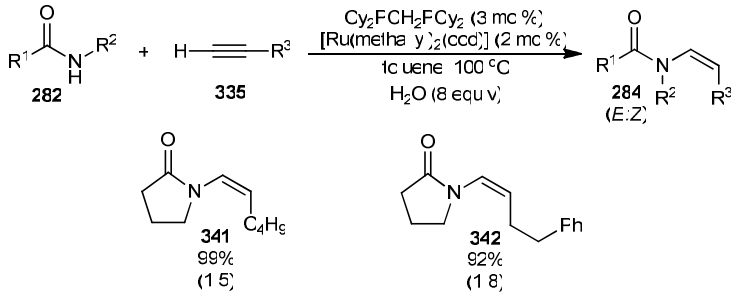

**Scheme 3.30**

In subsequent years, the Gooßen group has carried out a great deal of work in this area. In their first example they described the ruthenium-catalysed hydroamidation of a variety of secondary amides, anilides, lactams, ureas, bislactams and carbamates to a range of terminal alkynes (Scheme 3.31).[134]




**Scheme 3.31**

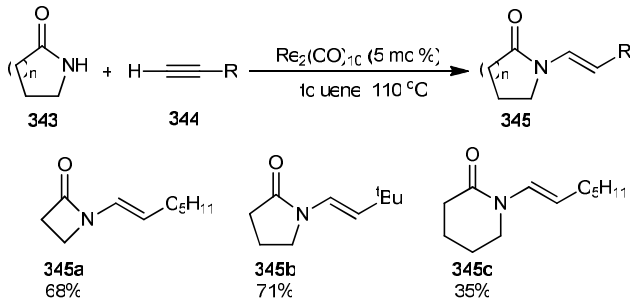
The first set of conditions yielded the *E*-enamide with a high level of stereoselectivity. However, the presence of an electron-rich chelating phosphane ligand and water was found to reverse the selectivity of the reaction to preferentially form the *Z*-enamide (Scheme 3.32).[134]




**Scheme 3.32**

The scope of this reaction was later extended to include primary amides[135] and imides[136] *via* the use of lanthanide-based Lewis acids. The group also addressed the issue of the prohibitive price of the first generation catalyst and soon afterwards reported a new protocol based on $RuCl_3 \cdot 3H_2O$ as the catalytic precursor.[137]

A rhenium-catalysed hydroamidation has also proved to be effective for the reaction of a limited range of cyclic amides with unactivated terminal alkynes (Scheme 3.33).[138]



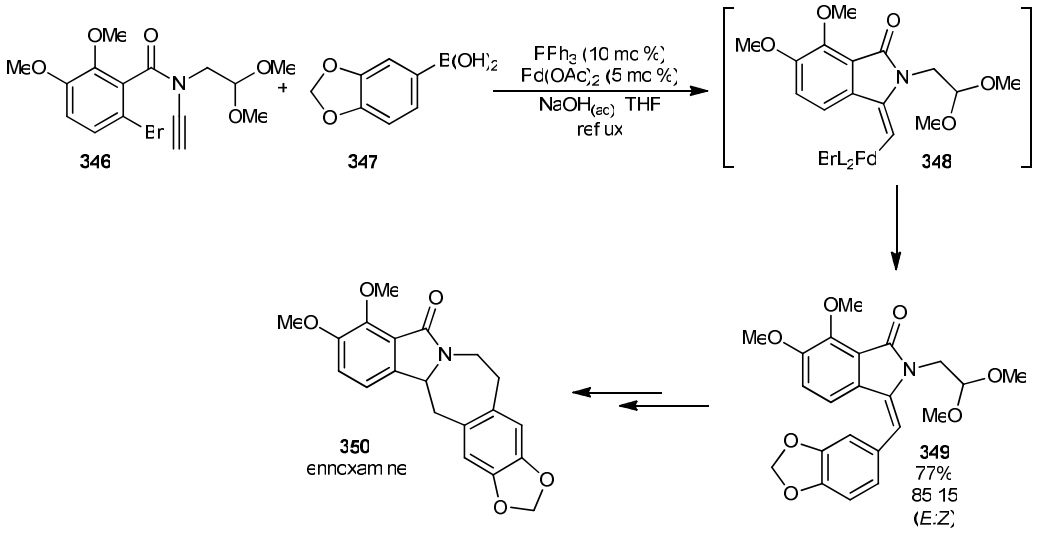

**Scheme 3.33**

From a green chemistry perspective, the hydroamidation of terminal alkynes is an ideal route to enamides, as the reaction is atom economic and additionally uses readily available starting materials. Unfortunately, although the stereoselectivity of the reaction can be carefully controlled, an inherent limitation of this methodology is that the use of terminal alkynes restricts the reaction scope to the preparation of β-monosubstituted enamides.

### 3.3.3 Use of Ynamide Starting Materials

Ynamides[139] are versatile synthetic intermediates that can undergo a variety of synthetic transformations to form enamides. Recently there has been increased interest in this approach to enamides, as ynamide synthesis has become more straightforward in light of developments in alkynyliodonium salt chemistry[140] and copper-[141] and iron-catalysed[142] alkynlation technologies.

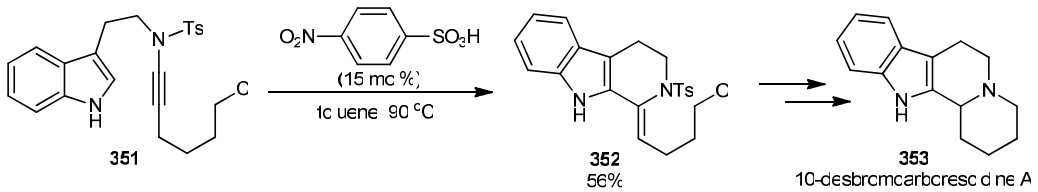
Representative intramolecular examples include the domino Heck–Suzuki–Miyaura reaction.[143] This transformation was used to great effect in the total synthesis of lennoxamine (Scheme 3.34).




**Scheme 3.34**

The palladium-catalysed intramolecular Heck reaction is followed by a cross-coupling with a boronic acid, which produces the intermediate **349**. The stereoselectivity of the reaction was not especially high but this was not an issue as a subsequent step involved the hydrogenation of the double bond isomers.

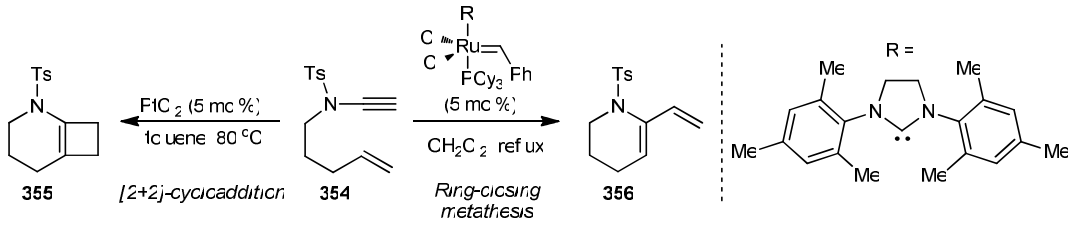
Another example of enamide synthesis *via* intramolecular transformations of ynamide substrates is the Brønsted acid-catalysed keteniminium cyclisation, a variant of the Pictet–Spengler cyclisation.[144] Application of this methodology to the synthesis of 10-desbromoarborescidine A was successful (Scheme 3.35).




**Scheme 3.35**

The critical Pictet–Spengler-type cyclisation takes place to give the tricyclic product **352** in 56% yield under Brønsted acid catalysis. Lewis acids were found to be ineffective in the desired transformation.

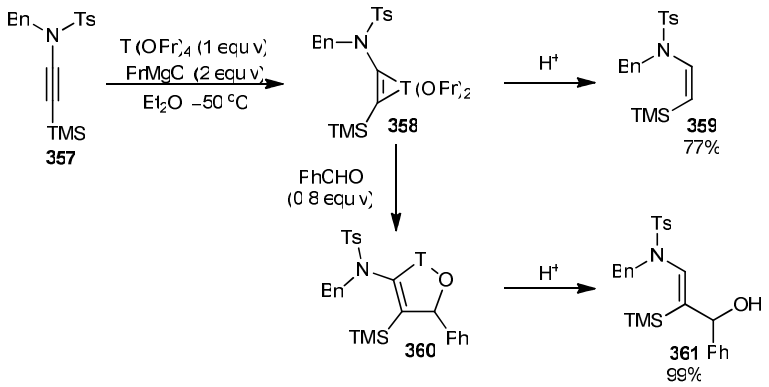
Enamides can also be constructed from the intramolecular reaction of ene-ynamides (Scheme 3.36).




**Scheme 3.36**

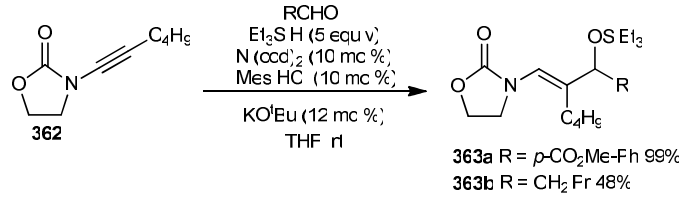
Platinum dichloride catalyses a formal [2+2] cycloaddition reaction to give a fused bicyclic system of low stability (**355**).[145] Conversely, Grubbs' second generation ruthenium catalyst[146] results in the ring closing metathesis products, containing dienamide moieties that were subsequently used in Diels-Alder investigations to construct polycyclic systems (**356**).[147]

In addition, it is possible to access enamides *via* intermolecular reactions of ynamides; reductive coupling reactions are such an example. Both titanium-mediated[148] and nickel-catalysed transformations[149] have been reported in recent years. In the titanium example (Scheme 3.37), an ynamide-titanium alkoxide **358** is formed, which can then undergo hydrolysis to produce the β-monosubstituted enamide **359** or react with an aldehyde to give the β,β-disubstituted enamide **361**.




**Scheme 3.37**

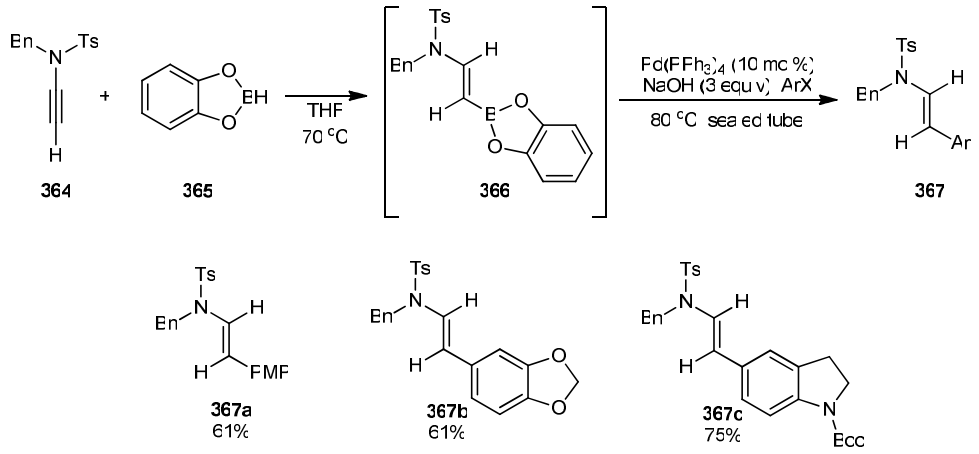
In the later nickel-based system, a catalytic multicomponent coupling of ynamides, aldehydes and silanes proceeds to yield the corresponding γ-siloxyenamides in a highly stereoselective fashion (Scheme 3.38).




**Scheme 3.38**

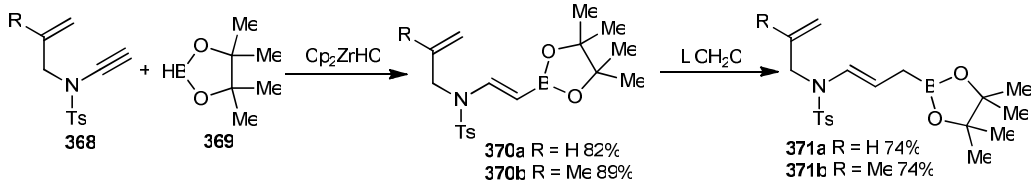
In many cases, reactions of ynamides can result in the formation of enamide derivatives that possess non-carbon substituents, such as boranes and halide groups. These derivatives can be interesting in themselves or can undergo further reaction to yield more highly all-carbon substituted enamides.

For instance, Witulski and co-workers described a hydroboration of ynamides followed by a Suzuki–Miyaura cross-coupling with aryl halides (Scheme 3.39).[150] In this case, it was unfavourable to isolate the hydroborated enamide intermediates and so a one-pot coupling reaction was developed.



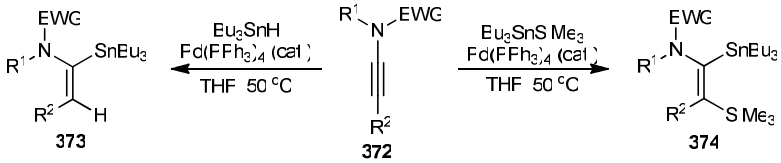

**Scheme 3.39**

Moreover, the homologation of enamide boronates was possible in the presence of chloromethyllithium and gave (*E*)-γ-aminoallylboronates in high yields (Scheme 3.40).[151]




**Scheme 3.40**

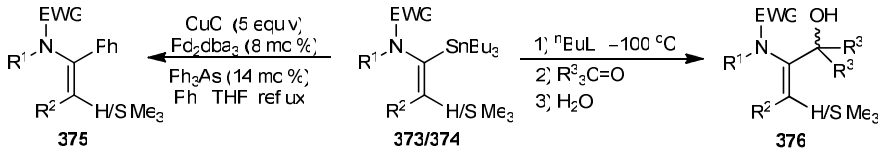
The Cintrat group have published a series of papers on the palladium-catalysed stannylation of ynamides to give both hydro- and silylstannylated enamides (Scheme 3.41).[152]




**Scheme 3.41**

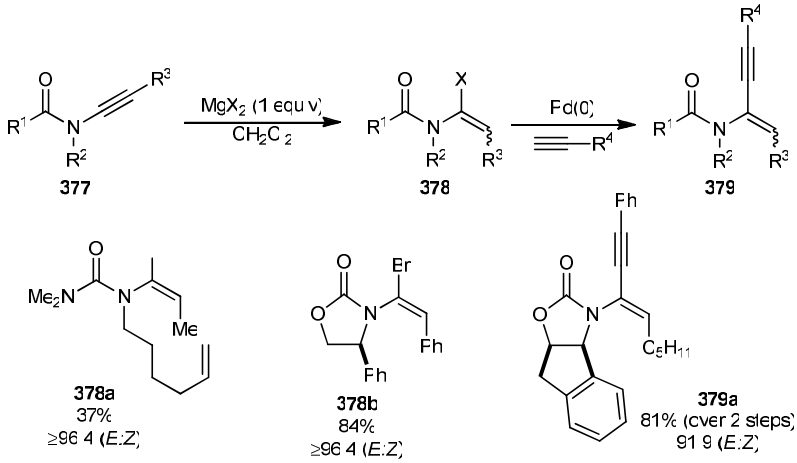
In the majority of cases, the reactions proceed with high levels of regio- and stereoselectivity. The α-substituted stannyl enamides are able to undergo Stille

couplings and lithiation-electrophilic trapping reactions to give more highly substituted enamide products (Scheme 3.42).




**Scheme 3.42**

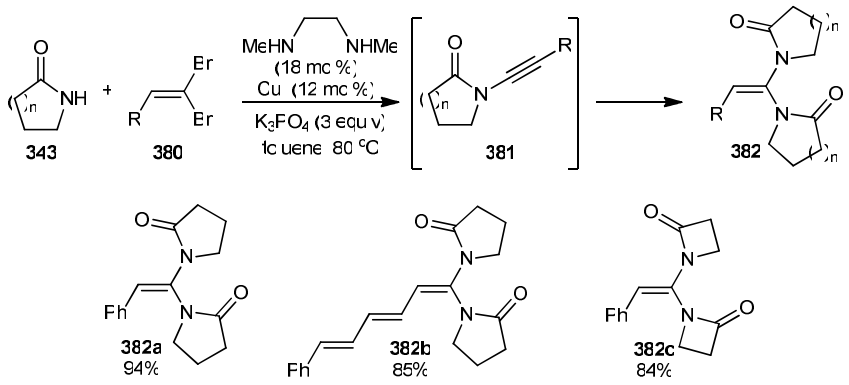
The hydrohalogenation of ynamides is able to take place under exceptionally mild conditions.[153] The resultant α-haloenamide products smoothly undergo Sonogashira coupling to give the α-alkynyl-substituted enamides (Scheme 3.43).




**Scheme 3.43**

Completely anhydrous conditions resulted in poor conversions to the desired products and the group hypothesised that HX is generated *in situ via* the reaction of the magnesium halide salt with trace amounts of water present in the solvent.

Recently Evano and co-workers described the formation of ketene *N,N*-acetals, a specific class of enamide (Scheme 3.44).[154]



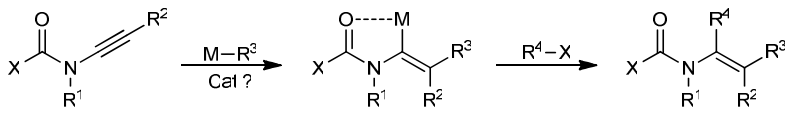

**Scheme 3.44**

In this instance, copper-catalysed monocoupling of 1,1-dibromo-1-alkenes with an amide and a subsequent dehydrobromination result in the formation of the ynamide. Under the reaction conditions, a hydroamidation then gives the observed enamide-like products.

It is clear from the review that although a plethora of effective methods exist for the synthesis of enamides from ynamide precursors, the majority are restricted to the production of certain classes of enamide.

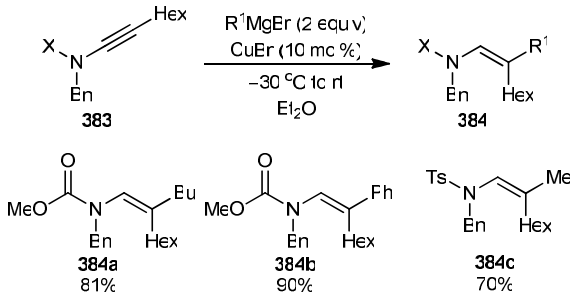
### *Carbometallation of Ynamides*

An alternative route to access enamides is the carbometallation[155] of ynamides; as the majority of carbometallation reactions proceed in a *syn*-selective manner,[155a] selectivity issues are reduced to those of regioselectivity (provided that no *E/Z* isomerisation occurs under the reaction conditions). In addition, there exists the potential to utilise the alkenyl metal intermediates in further functionalisation reactions, to theoretically allow the preparation of more complex enamide products (Scheme 3.45).



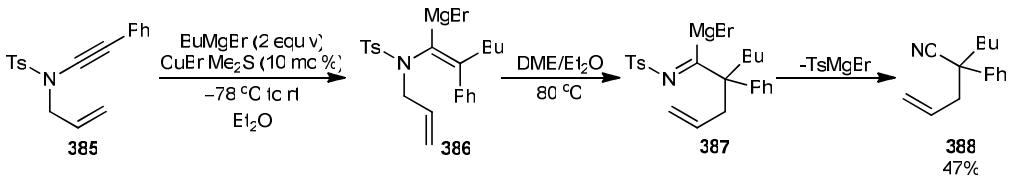

**Scheme 3.45**

Marek and co-workers pioneered the strategy of carbometallation of ynamides when they described the first carbocupration and the first copper-catalysed carbomagnesiation of yne-sulfonamides.[156] As previously surmised, the reaction was highly regioselective and this was attributed to the coordination of the copper to the oxygen of the sulfonamide in the non-polar solvent (Scheme 3.46).



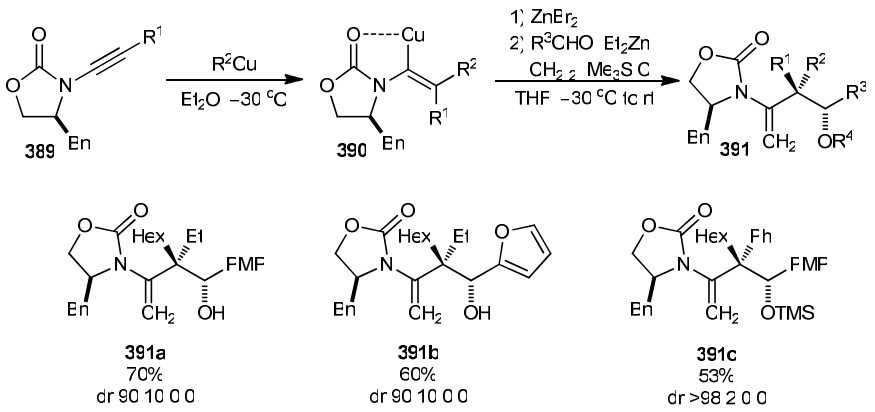

**Scheme 3.46**

Consequently other groups used this novel technology in the copper-catalysed carbomagnesiation of ynamides, to produce intermediates that undergo aza–Claisen rearrangements to form 4-pentenenitriles (Scheme 3.47).[157]




**Scheme 3.47**

More recently the Marek group have exploited their methodology in a novel approach to aldol products containing all-carbon quaternary stereocentres (Scheme 3.48).[158]




**Scheme 3.48**

Regioselective carbometallation of an enantiomerically pure ynamide results in the formation of the vinyl copper intermediate **390** that is readily homologated with an organozinc reagent and then allylated to give the aldol derivative **391**. The presence of $R_3SiCl$ in the reaction mixture prevents an undesired side reaction and the enamide products are isolated as silyl enol ethers, which give the alcohol derivatives after acidic hydrolysis.

## 3.4 Conclusions

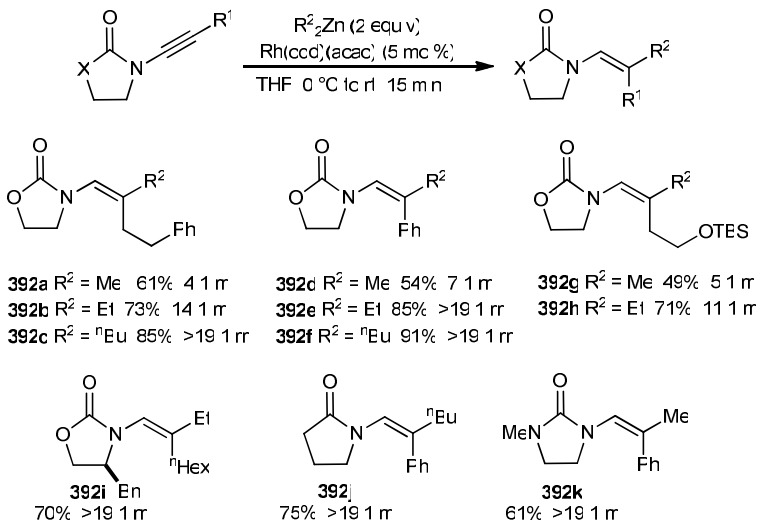
It is clear from this review that enamides are valuable commodities in organic synthesis thanks to their long-term stability and wide-ranging reactivity. Furthermore, the enamide motif is present in many biologically active compounds. Consequently their synthesis is an important area of study. Recent strategies of enamide preparation include transition metal-catalysed *N*-alkenylation and hydroamidation reactions. Despite the ready preparation of enamides in a stereoselective fashion, both methods suffer drawbacks; the cross-coupling method necessitates the often non-trivial stereoselective preparation of vinyl halides and the hydroamidation route is inherently restricted to the synthesis of β-monosubstituted enamides. After pioneering work by the Marek group, ynamide carbometallation is clearly emerging as an effective route to access multisubstituted enamides, although there remains scope for improvement. The current methods rely on the use of Grignard reagents as the organometallic species; this restricts the use of base- or

nucleophile-sensitive functional groups on both the substrate and the organometallic reagent itself.[159] Therefore the development of alternative carbometallation procedures, to complement the existing protocols, is highly desirable.

# 4.0 Rhodium-Catalysed Carbometallation and Hydrometallation of Ynamides to Access Multisubstituted Enamides[i]

## 4.1 Background

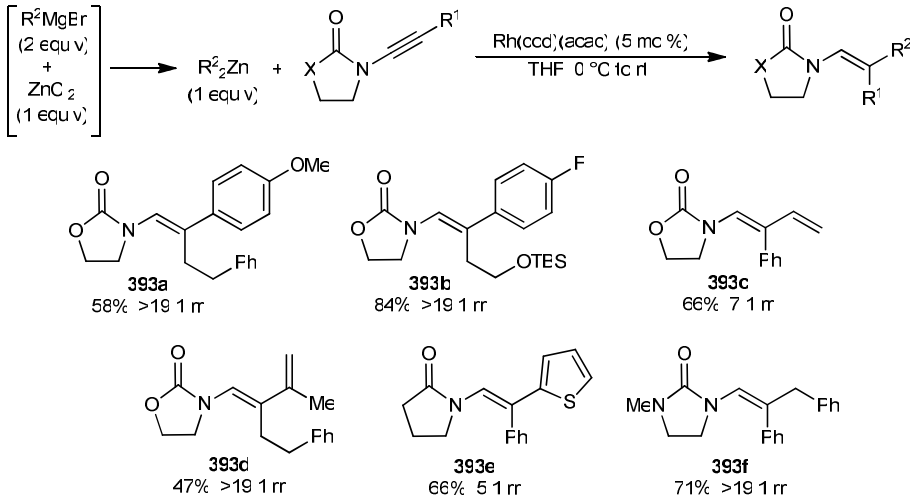
Our group recently reported a highly efficient rhodium-catalysed carbozincation of ynamides in the synthesis of multisubstituted enamides (Scheme 4.1).[160]




**Scheme 4.1**

In the initial study, dialkylzinc reagents were employed as the organometallic species and this allowed the highly regio- and stereoselective preparation of a range of β,β-disubstituted enamides containing oxazolidin-2-one, pyrrolidin-2-one and urea moieties. The use of dialkylzinc reagents limited the methodology to the small number that were commercially available; a wider variety of products were accessible *via* the *in situ* preparation of diorganozinc species from Grignard reagents and zinc chloride (Scheme 4.2).[160]

[i] The work in this chapter was carried out in collaboration with Benoit Gourdet. The experiments to make **394b**, **394c**, **394g** and **395c** (Scheme 4.3), **396f** (entry 6, Table 4.1), **400a** and **400b** (Method A, Scheme 4.5), **412** (Scheme 4.9) and **416a** and **416b** (Scheme 4.10) were carried out by him. In all cases, these experiments have been denoted with an asterix (*) and a footnote. The remainder of the work is my own.




**Scheme 4.2**

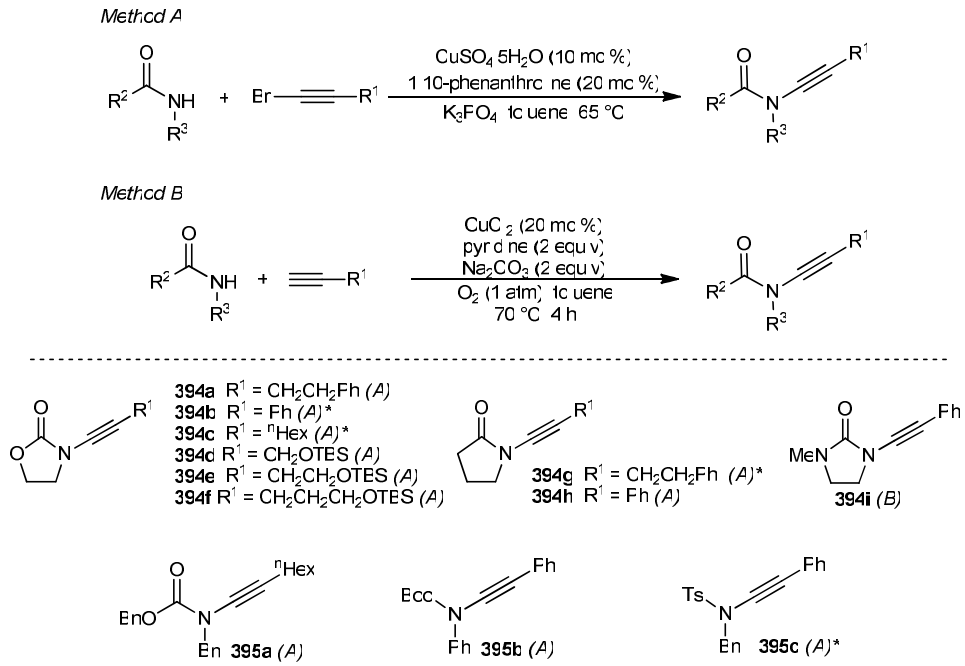
Aromatic, heteroaromatic, alkenyl and benzyl groups were all successfully introduced under rhodium catalysis, although in some examples (**393c** and **393e**) the reactions were carried out at –78 °C to achieve satisfactory regioselectivities.

These initial results were highly promising and it was considered worthwhile to fully explore the scope and limitations of this catalytic system, in terms of the organometallic species, the ynamide substrate and the rhodium catalyst.

## 4.2 Results and Discussion[161]

### 4.2.1 Preparation of Ynamide Substrates

Recent advances in copper-catalysed coupling reactions of amides with bromoalkynes or terminal alkynes have greatly increased the range of ynamides that are easily prepared.[162] The ynamides examined in the current investigation and the two methods used for their preparation are illustrated in Scheme 4.3.




**Scheme 4.3**

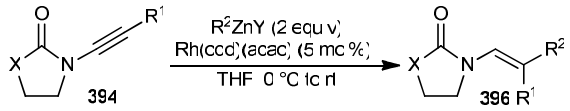
The majority of ynamides were synthesised using method A,* in which a bromoalkyne is coupled to an amide.[162a] Despite being an effective method for the synthesis of a wide range of ynamides, we observed a lack of reproducibility in the yields, a trend that has been reported by other groups.[163] A recent investigation into the reasons for these irregularities has attributed the lower yields to 'wet' potassium phosphate reagents i.e. those contaminated with significant amounts of $K_3PO_4 \cdot 1.5H_2O$ and $K_3PO_4 \cdot 7H_2O$.[164] Detailed studies revealed that pure and anhydrous $K_3PO_4$ provides higher yields of the desired ynamide.[164] Stahl devised an alternative route to ynamides *via* the coupling reaction of amides with terminal alkynes, under oxidative conditions.[162c] The scope of this reaction is slightly more restricted than Hsung's protocol and requires five equivalents of the amide component, but it was effectively employed for the urea-containing ynamide **394i**.

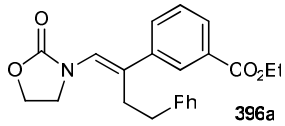
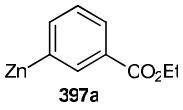
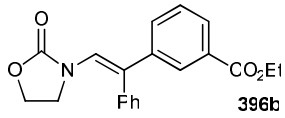
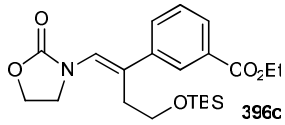
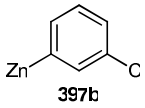
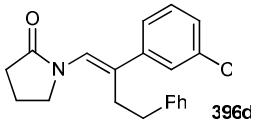
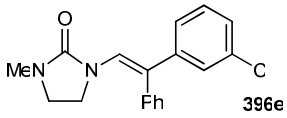
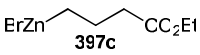
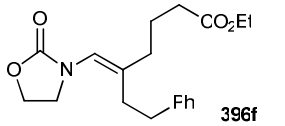
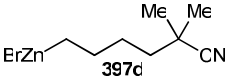
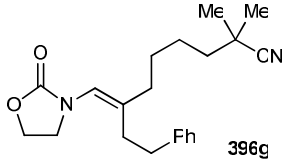
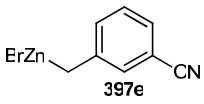
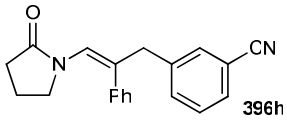
### 4.2.2 Expansion to Organozinc Halide Reagents

The reliance of the rhodium-catalysed carbozincation reaction on commercially available dialkylzinc reagents had initially restricted the scope of the reaction; the *in*

* Substrates **394b**, **394c**, **394g** and **395c** were prepared by Benoit Gourdet.

*situ* preparation of diorganozinc reagents from $ZnCl_2$ and Grignard reagents had partly resolved this issue and enlarged the pool of enamides that could be synthesised using this methodology. Unfortunately the use of Grignard reagents limits the presence of base- and nucleophile-sensitive functional groups on the organometallic species. Therefore, it was highly desirable to extend the scope of the organometallic component to include functionalised organozinc halide reagents (Table 4.1).




| entry | ynamide | $R^2ZnY$ | product | rr[a] | Yield (%)[b] |
|---|---|---|---|---|---|
| 1 | **394a** | |  **396a** | >19:1 | 75 |
| 2 | **394b** |  **397a** |  **396b** | >19:1 | 58 |
| 3 | **394e** | |  **396c** | >19:1 | 66 |
| 4 | **394g** |  **397b** |  **396d** | >19:1 | 77 |
| 5 | **394i** | |  **396e** | >19:1 | 82 |
| 6[*] | **394a** |  **397c** |  **396f** | >19:1 | 54 |
| 7 | **394a** |  **397d** |  **396g** | 4:1 | 45[c] |
| 8 | **394h** |  **397e** |  **396h** | n.d.[d] | 35[e] |

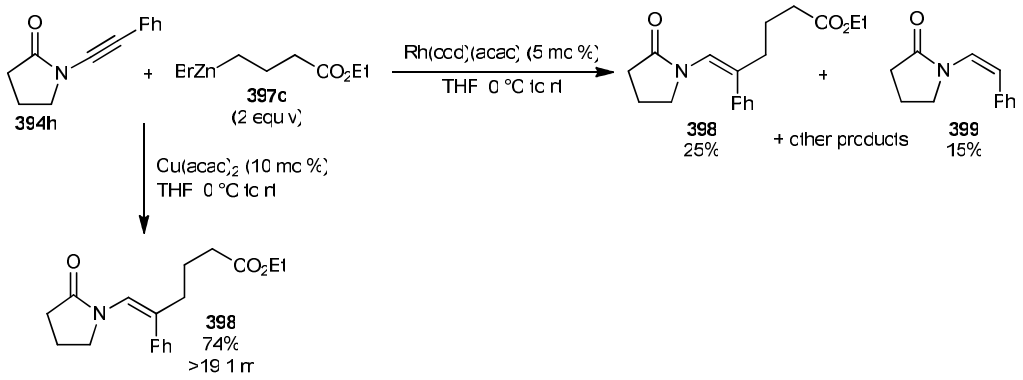
[a] rr = Regioisomeric ratio as determined by $^1H$ NMR analysis of the unpurified reaction mixtures. [b] Isolated yield of major regioisomer. [c] The hydrometallation product **401** was also isolated in 12% yield. [d] The ratio of isomers could not be determined due to the complexity of the unpurified reaction mixture. [e] Result obtained using $[Rh(cod)Cl]_2$ (5 mol%) and *rac*-BINAP (10 mol%) at 60 °C for 6 h.

**Table 4.1**

[*] This experiment was carried out by Benoit Gourdet.

Fortuitously, the reaction conditions were compatible with the use of organozinc halides and we applied them to a range of ynamide substrates (Table 4.1). Aromatic zinc iodide reagents bearing an ester group or a chloro group resulted in the desired enamides in good to high yields with excellent regioselectivities (entries 1-5). In addition, aliphatic zinc bromides could be employed as the organometallic component (entries 6 and 7). However, a relatively low yield of the desired enamide was observed when the nitrile-containing zinc bromide **397d** was employed. This was attributed to the low regioselectivity observed during the carbometallation reaction and the formation of the hydrometallation side-product. A slight modification of the reaction conditions (including a higher temperature) was required when the cyanobenzyl zinc bromide **397e** was used as the carbometallating agent. Despite these adjustments, the crude reaction contained a complex mixture of unidentified products and the desired enamide **396h** was isolated in a low yield.

In the case of the pyrrolidin-2-one-derived ynamide **394h**, the rhodium-catalysed carbozincation conditions resulted in a significant degree of the hydrometallation product **399** along with other unidentified products. Replacing the rhodium catalyst with a copper catalyst allowed the clean preparation of the enamide **398** with high regioselectivity and no hydrometallation was observed (Scheme 4.4).




**Scheme 4.4**

However, the copper catalyst did not function effectively in the carbometallations involving aromatic zinc halide reagents and in these cases unreacted starting materials were recovered.

X-ray crystallography of the β,β-diaryl substituted enamide **396b** established the regioselectivity of the carbometallation reaction with the arylzinc halide **397a** (Fig 4.1). The remainder of enamide products were assigned by analogy.

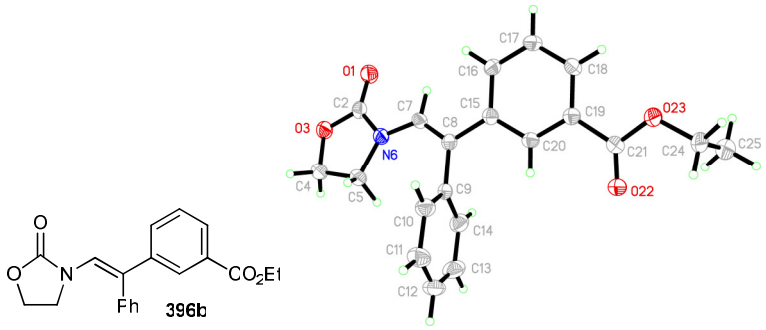



**Figure 4.1**

### 4.2.3 Acyclic Ynamides

To increase the utility of our methodology, it was desirable to investigate our rhodium-catalysed carbozincation conditions in conjunction with a more diverse range of ynamides. The methodology had proven its effectiveness with ynamides containing oxazolidin-2-one, pyrrolidin-2-one and urea moieties, in which the amide functionality was fixed in a five-membered ring. We next chose to evaluate acyclic ynamides, such as **395a**, **395b** and the yne-sulfonamide **395c** (Fig 4.2).

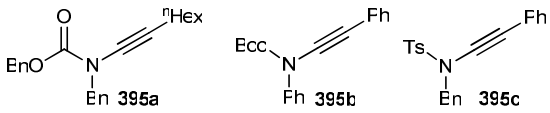
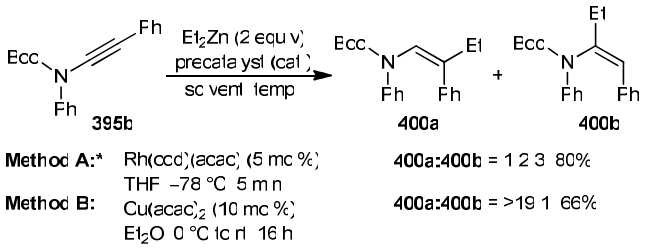



**Figure 4.2**

Ynamide substrates containing an aliphatic substituent at the β-position (such as **395a**) appeared to be largely inert under our standard rhodium-catalysed conditions with $Et_2Zn$, although a small degree of substrate decomposition was observed over extended reaction times. Phenyl-substituted ynamides proved to be far more reactive

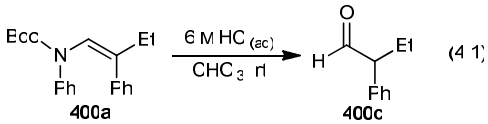
and the carbozincation reactions went to full conversion rapidly, even at decreased temperatures (**395b** and **395c**). Unfortunately the reactions suffered from low regioselectivities, despite these lower temperatures. For the Boc-protected ynamide (**395b**) the corresponding enamides were isolated as a regioisomeric mixture, marginally in favour of the unexpected regioisomer **400b** (Method A, Scheme 4.5).* The yne-sulfonamide **395c** gave similar results but these products were not isolated.




**Scheme 4.5**

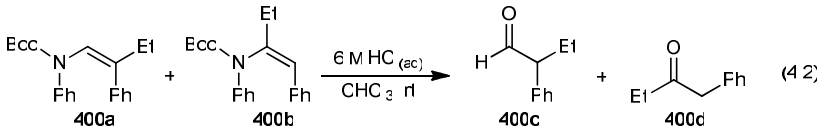
Fortunately, a $Cu(acac)_2$ catalyst, which had previously been used advantageously in partnership with the aliphatic zinc bromide **397c** (*vide supra*), provided the desired enamide with high regioselectivity; although reaction times were extended significantly. However, it offered no further improvement for the other ynamide substrates **395a** and **395c**, which both remained unchanged when subjected to the new conditions.

The isomeric composition of the carbometallation reactions depicted in Scheme 4.5 was determined *via* acidic hydrolysis of the enamide products. The enamide **400a** (isolated from Method B, Scheme 4.5) provided the aldehyde **400c** after treatment with HCl (eq 4.1).




However, hydrolysis of the mixture of enamides **400a** and **400b** (obtained *via* method A, Scheme 4.5) resulted in both the aldehyde **400c** and the ketone **400d** (eq 4.2).

* This experiment was carried out by Benoit Gourdet.



(4.2)

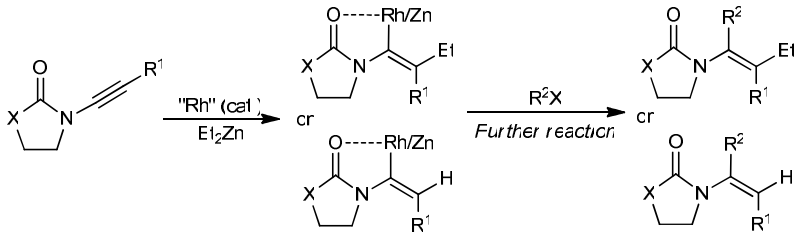
These results indicated the relationship between the enamides **400a** and **400b** was regioisomeric rather than stereoisomeric.

Attempts to extend the carbozincation of the ynamide **395b** to the use of aliphatic organozinc halides with either Rh(cod)(acac) or $Cu(acac)_2$ catalysts were unsuccessful. Complex mixtures of products were obtained in both cases and, for the copper-based procedure, low conversions were observed. Employing aromatic zinc halides as the organometallic species for the carbometallation of acyclic ynamides gave no reaction.

It is reasonable to assume that the high regioselectivity previously observed for the cyclic ynamides is due to the directing group effect of the carbonyl group with the rhodium (and/or zinc) centre in the carbometallation step (see later for a full mechanistic discussion). The acyclic ynamides **395a**, **395b** and **395c** all possess a greater degree of rotational freedom and this may lessen the ability of the carbonyl (or sulfonyl) group to direct the metal centre, thus resulting in a lower regioselectivity for these substrates.

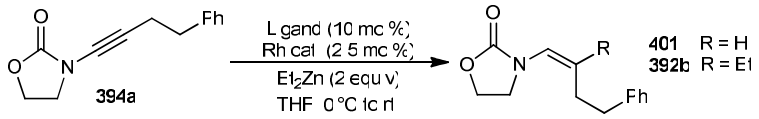
### 4.2.4 Ligand Effects

During the course of these investigations, hydrometallation products were observed in the reactions of certain organozinc species containing a β-hydrogen (see Table 4.1, entry 7 and Scheme 4.4, **399**). Development of a completely complementary rhodium-catalysed hydrometallation procedure was highly desirable. Although other routes to access β-monosubstituted (*Z*)-enamides exist,[131, 134] further reaction of an alkenyl zinc intermediate would allow the preparation of multisubstituted enamides of different substitution patterns (Scheme 4.6).




**Scheme 4.6**

Preliminary studies assessed the activity of different rhodium sources in comparison to the standard Rh(cod)(acac) catalyst with the model substrate **394a**. Both $[Rh(cod)Cl]_2$ and the cationic $[Rh(cod)(MeCN)_2]BF_4$ resulted in full conversion to the carbometallation enamide product (Table 4.2, entries 2 and 3). However, in the presence of Wilkinson's catalyst, a 5:1 mixture of the hydrometallation and carbometallation products was obtained (entry 4). It was hypothesised that the presence of the phosphine ligands on the rhodium centre moderated its catalytic activity to favour the hydrometallation pathway. Therefore a series of phosphine ligands were examined in conjunction with $[Rh(cod)Cl]_2$ in the reaction of the model substrate **394a** (Table 4.2).




| entry[a] | Rh Cat. | ligand | 401:392b[b] |
|---|---|---|---|
| 1 | Rh(cod)(acac) | — | <1:19 |
| 2 | $[Rh(cod)(MeCN)_2]BF_4$ | — | <1:19 |
| 3 | $[Rh(cod)Cl]_2$ | — | <1:19 |
| 4 | $RhCl(PPh_3)_3$ | — | 5:1 |
| 5 | $[Rh(cod)Cl]_2$ | $Ph_3P$ | 9:1[d] |
| 6 | $[Rh(cod)Cl]_2$ | $Bu_3P$ | <1:19 |
| 7 | $[Rh(cod)Cl]_2$ | *(rac)*-BINAP | <1:19 |
| 8 | $[Rh(cod)Cl]_2$ | $(p\text{-F-Ph})_3P$ | >19:1[c] |
| 9 | $[Rh(cod)Cl]_2$ | $(2\text{-Thienyl})_3P$ | >19:1[c] |
| 10 | $[Rh(cod)Cl]_2$ | $(2\text{-Fur})_3P$ | 12:1 |
| 11 | — | — | <1:19[d] |

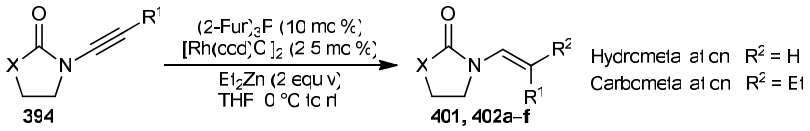
[a] All reactions proceeded to complete conversion. Carbometallation product **392b** was generally obtained in ≥19:1 regioisomeric ratio. [b] Ratios determined by $^1H$ NMR analysis of the unpurified reaction mixtures. [c] Hydrometallation product **401** had a stereoisomeric composition of *ca.* 10:1 *Z*:*E*. [d] Reaction proceeded to 10% conversion after 5 h.

**Table 4.2**

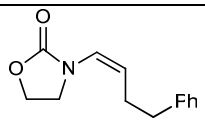
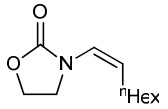
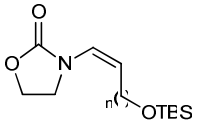
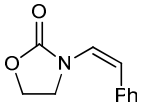
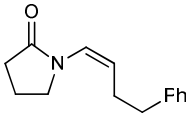
Triphenylphosphine-modified $[Rh(cod)Cl]_2$ further favoured the formation of the hydrometallation product (entry 5). However, the use of the strongly σ-donating ligand ($Bu_3P$, entry 6) and a bidentate ligand (*rac*-BINAP, entry 7) reversed the selectivity of the reaction back towards the carbometallation product. Further investigations revealed that good π-acceptor ligands (entries 8-10) facilitated the desired hydrometallation pathway with high selectivity. The use of $(p\text{-F-Ph})_3P$ (entry 8) and $(2\text{-thienyl})_3P$ (entry 9) both produced minor quantities of the (*E*)-isomer of **401**. $(2\text{-Fur})_3P$ (entry 10) gave the cleanest reaction and was selected for further study. Additional optimisation studies were carried out which included variation of solvent, temperature and ligand-to-metal ratios; unfortunately it was not possible to improve the selectivity further. Significantly, the rate of reaction was greatly

diminished in the presence of the phosphine-modified catalysts (up to 6 h for complete conversion). Therefore it is possible that a slow uncatalysed background reaction is responsible for the small amounts of **392b** observed in some of these hydrometallation reactions (entry 11).

With the optimised hydrometallation conditions in hand, the scope of the reaction was examined with a range of ynamide substrates (Table 4.3).




394 401, 402a–f

| entry | ynamide | product | | selectivity[a] | yield (%)[b] |
|---|---|---|---|---|---|
| 1 | **394a** |  | **401** | 12:1 | 60[c] |
| 2 | **394c** |  | **402a** | 11:1 | 46 |
| 3 | **394d** |  n = 1 | **402b** | 9:1 | 58 |
| 4 | **394e** | n = 2 | **402c** | 6:1 | 58[d] |
| 5 | **394f** | n = 3 | **402d** | 6:1 | 42 |
| 6 | **394b** |  | **402e** | 6:3(:1)[e] | –[f] |
| 7 | **394g** |  | **402f** | 16:1 | 53[d] |

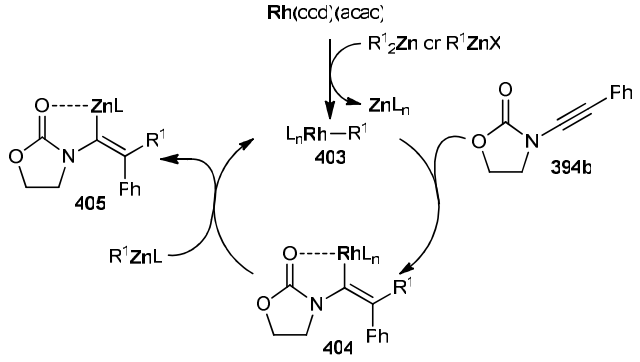
[a] Selectivity = ratio of hydrometallation ($R^2$ = H) to carbometallation ($R^2$ = Et) as determined by $^1$H NMR analysis of the unpurified reaction mixtures. [b] Unless otherwise stated, isolated yield of an inseparable mixture of hydrometallation and carbometallation product in a ratio identical to that measured from the unpurified reaction mixtures. [c] Isolated yield of a 9:1 mixture of hydrometallation product **401** and carbometallation product **392b**. [d] Isolated yield of pure hydrometallation product. [e] The *E*-hydrometallation product was also detected (proportion in parentheses). [f] The complex mixture was not purified.

**Table 4.3**

Ynamide substrates with an aliphatic group at the β-position were well tolerated under the reaction conditions, providing the hydrometallation products in good selectivities and reasonable yields (entries 1-5 and 7). An aromatic β-substituent unfortunately resulted a dramatic decrease in the selectivity of the reaction and a significant quantity of the (*E*)-isomer of the hydrometallation product was also formed (entry 6). Both oxazolidin-2-one (entry 1-6) and pyrrolidin-2-one (entry 7) moieties in the ynamide substrate were compatible with the reaction conditions. Unfortunately, in the majority of cases it was not possible to completely separate the hydrometallation product from the carbometallation product *via* column chromatography and so these substrates were isolated as mixtures.

### 4.2.5 Mechanistic Discussion

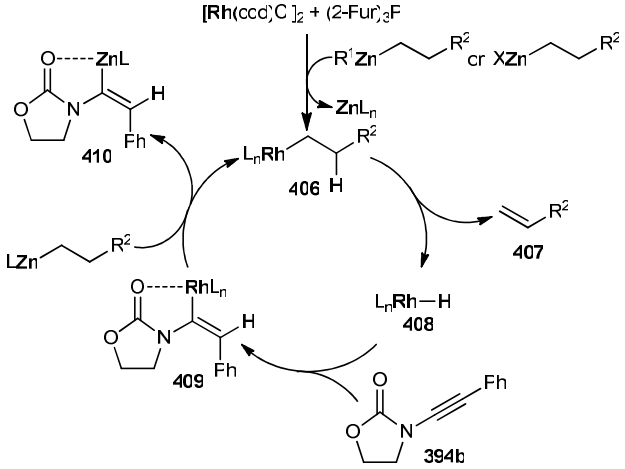
Our proposed mechanisms for the rhodium-catalysed carbometallation and hydrometallation of ynamides are outlined in Scheme 4.7 and Scheme 4.8 respectively. The mechanisms are depicted using the model substrate **394b** for illustrative purposes.




**Scheme 4.7**

Reaction of the Rh(cod)(acac) precatalyst with the zinc reagent generates the organorhodium intermediate **403** which undergoes a *syn*-carbometallation of the ynamide. It is presumed that the regioselectivity of the carbometallation step is governed by the directing group effect of the carbonyl functionality.

Transmetallation with an organozinc species allows regeneration of the active catalyst and liberates the alkenyl zinc intermediate **405**, which is protonated upon work-up.




**Scheme 4.8**

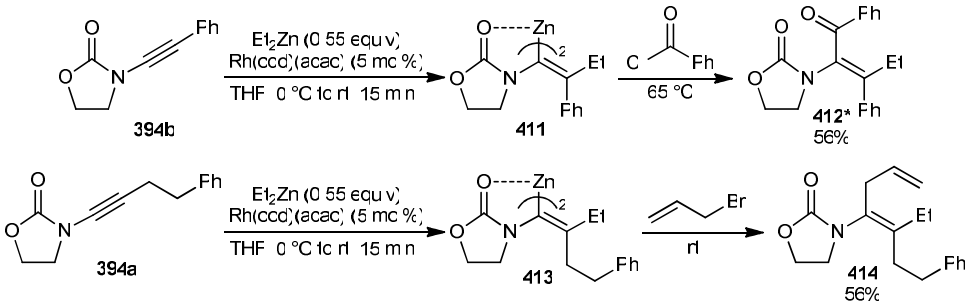
In the complementary hydrometallation reaction (Scheme 4.8), it is assumed that when a β-hydrogen is present in the organorhodium species **406**, the altered electronic properties of the phosphine-modified rhodium centre facilitate a β-hydride elimination to yield the rhodium hydride species **408**, which is then able to execute the hydrometallation step in a *syn*-fashion. Transmetallation with an organozinc species regenerates the active catalyst and the alkenyl zinc intermediate **410**.

### 4.2.6 Elaboration of Alkenyl Zinc Intermediates

In the proposed mechanisms for the rhodium-catalysed carbo- and hydrometallation of ynamides, the catalytic cycles liberate alkenyl zinc intermediates **405** and **410**. In order to synthesise more highly substituted enamides it was desirable to engage these species in further functionalisation reactions.

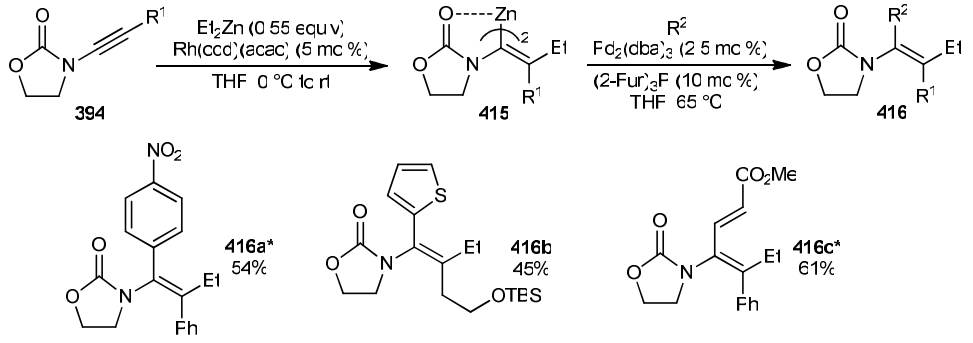
Initially the reaction of these alkenyl zinc species with electrophilic species was investigated. It was found that the carbozincation of ynamide **394b** with 0.55 equivalents of $Et_2Zn$ could be followed with an acylation reaction with benzoyl

chloride in a one-pot procedure to afford the α,β,β-trisubstituted enamide **412**[*] (Scheme 4.9). In a similar fashion, post-carbometallation the ynamide **394a** was trapped with allyl bromide to give the enamide **414** in a 56% yield (Scheme 4.9).




**Scheme 4.9**

Furthermore, alkenyl zinc species can participate in palladium-catalysed Negishi cross-coupling reactions.[165] Within the context of carbozincations using $Et_2Zn$, the tandem carbometallation–Negishi reaction proved to be effective with aromatic,[*] heteroaromatic and alkenyl iodides[*] to give the desired α,β,β-trisubstituted enamides in good yields over the two steps (Scheme 4.10).

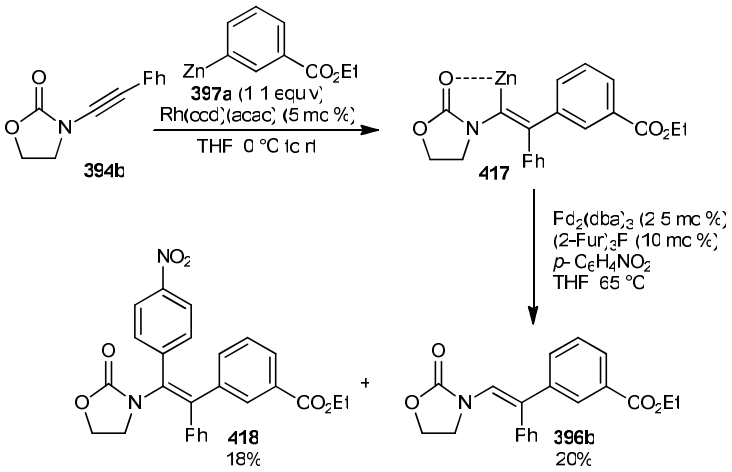



**Scheme 4.10**

Expansion of the tandem carbozincation–Negishi reaction to include the use of aromatic zinc iodides was feasible and the highly sterically hindered α,β,β-triaryl-substituted enamide **418** was made in this way. The reaction was low yielding and a significant quantity of the uncoupled carbometallation product was also isolated; this

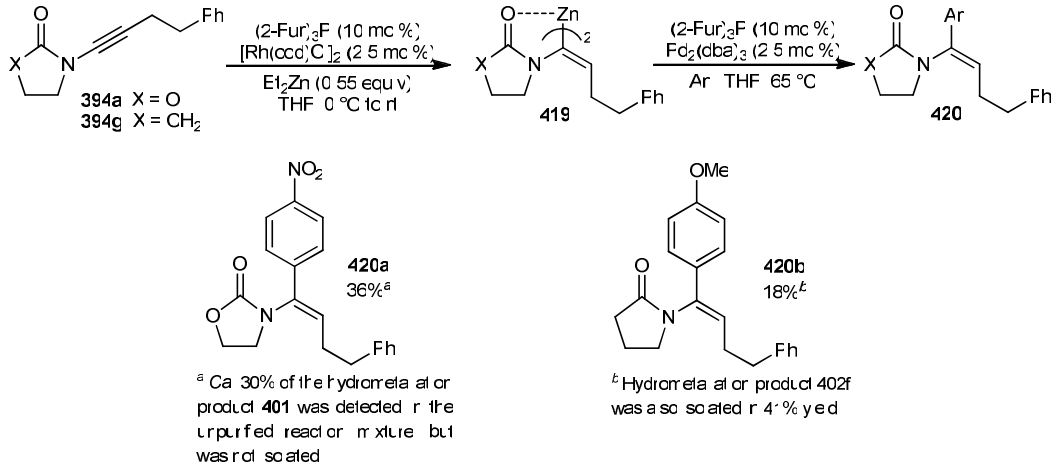
[*] These experiments were carried out by Benoit Gourdet.

was not surprising considering the steric hindrance that must be overcome in order for the Negishi reaction to take place (Scheme 4.11).




**Scheme 4.11**

Finally, the tandem hydrozincation–Neghisi reaction was investigated; lower yields of the α,β-disubstituted enamides were observed for these transformations (Scheme 4.12).




**Scheme 4.12**

It was unclear what factor resulted in the low conversions of these hydrozincated intermediates in the Negishi coupling. Extensive optimisation studies on the model ynamide **394a** with 4-iodonitrobenzene were unable to improve upon the yields. A

possible explanation could lie in the altered nature of the rhodium species in the hydrometallation manifold having a deleterious effect on the palladium-catalysed cross-coupling process.

## 4.3 Conclusions

We have developed a highly efficient stereo- and regioselective rhodium-catalysed carbozincation of ynamides as a method of preparing enamides. Studies have demonstrated that commercially available dialkylzinc reagents as well as those prepared *in situ* from Grignard reagents and organozinc halide reagents are able to act as effective carbometallating agents. Extension to acyclic ynamide substrates has been challenging as these reactions show a low regioselectivity under our rhodium-catalysed conditions. Furthermore, investigations into ligand effects have revealed that π-acceptor phosphine ligands mediate the catalytic activity of the rhodium metal, which then facilitates a hydrometallation pathway in preference to the carbometallation. We have been able to exploit the alkenylzinc intermediates produced during the course of these carbo- and hydrometallation processes in reactions with electrophilic species and in cross-coupling reactions, which has allowed the preparation of multisubstituted enamides.

# 5.0 Rhodium-Catalysed Carbometallation–Conjugate Addition Reaction[i]

## 5.1 Background

The utility of the indene nucleus is widely recognised (Fig 5.1); indenylmetallocene complexes are active catalysts in olefin polymerisation,[166,167] indene derivatives have been used in materials chemistry (in conducting polymers[168] and discotic liquid crystals[169]) and it is present in a number of biologically active compounds,[170] for example a series of 2,3-diarylindenes bind with high affinity to several estrogenic receptors (**423**, Fig 5.1).[170a]

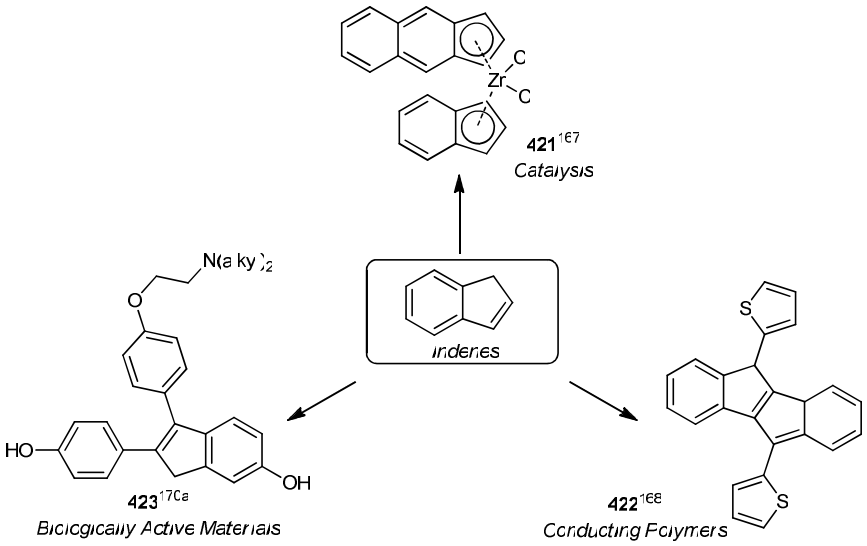
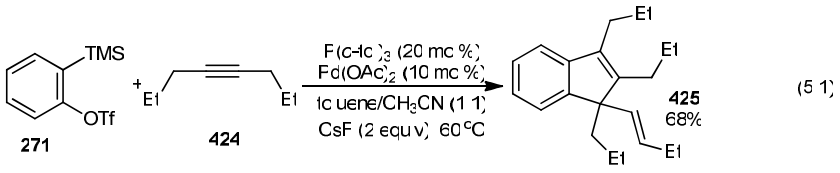



**Figure 5.1**

Highly substituted indene derivatives are commonly synthesised *via* transition metal-catalysed multicomponent cyclisation reactions, frequently involving alkynes.[171-175, 178] An early example of one such reaction was reported by Yamamoto and co-workers (eq 5.1).[171]

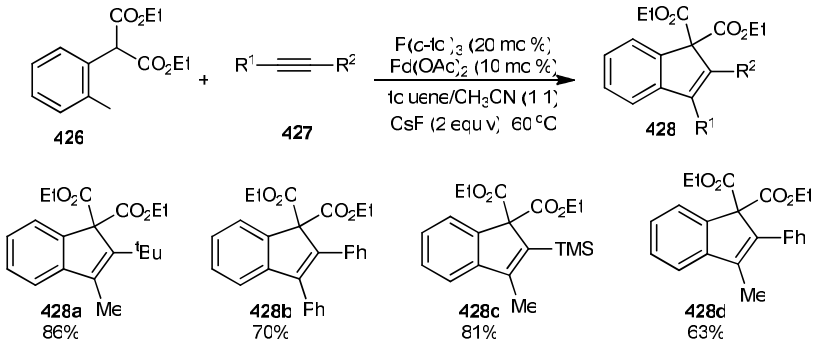
[i] The work in this chapter was carried out in collaboration with Benoit Gourdet. The experiments to prepare **443** (eq 5.2) and ligands **457a–e** (Table 5.2) were carried out by him. In all cases, these experiments have been denoted with an asterix (*) and a footnote. The remainder of the work is my own.



(5.1)

In the mixed toluene/acetonitrile solvent, the benzyne precursor **271** reacts with two molecules of alkyne to provide the highly substituted indene derivative in a reasonable yield.

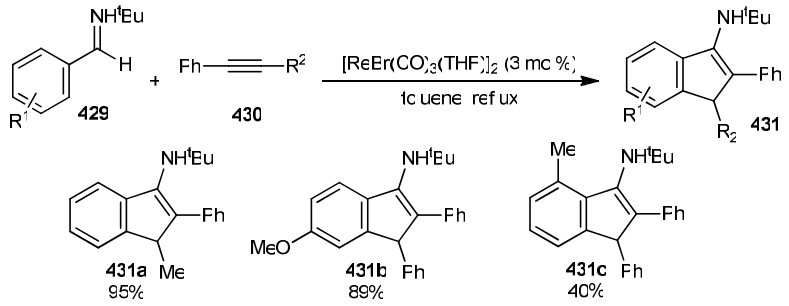
The Larock group has also employed the palladium-catalysed carboannulation of alkynes as an effective route to multisubstituted indenes (Scheme 5.1).[172]




**Scheme 5.1**

A diverse range of alkynes was subjected to the reaction conditions and high regioselectivities were observed for the unsymmetrical alkyne substrates.

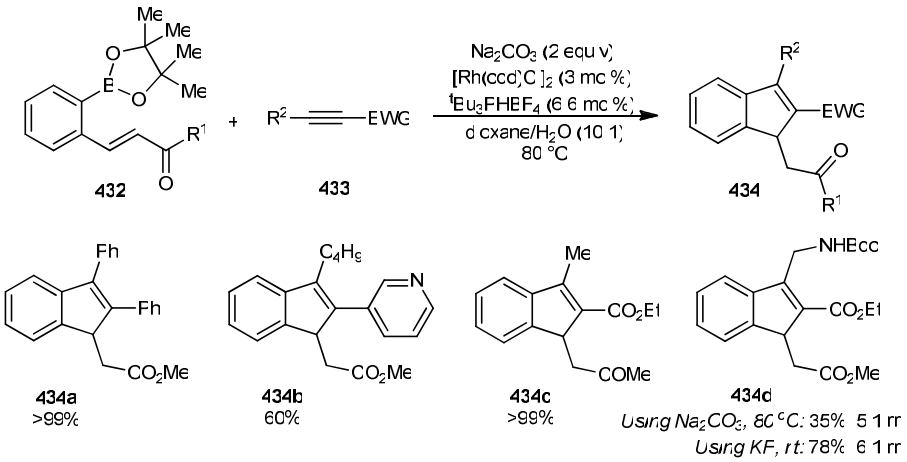
A rhenium complex is able to catalyse the coupling reaction of aromatic aldimines and phenylacetylenes to construct indene derivatives (Scheme 5.2).[173]




**Scheme 5.2**

Experimental evidence suggested that the reaction went *via* a C–H bond activation as the first step of the mechanism.

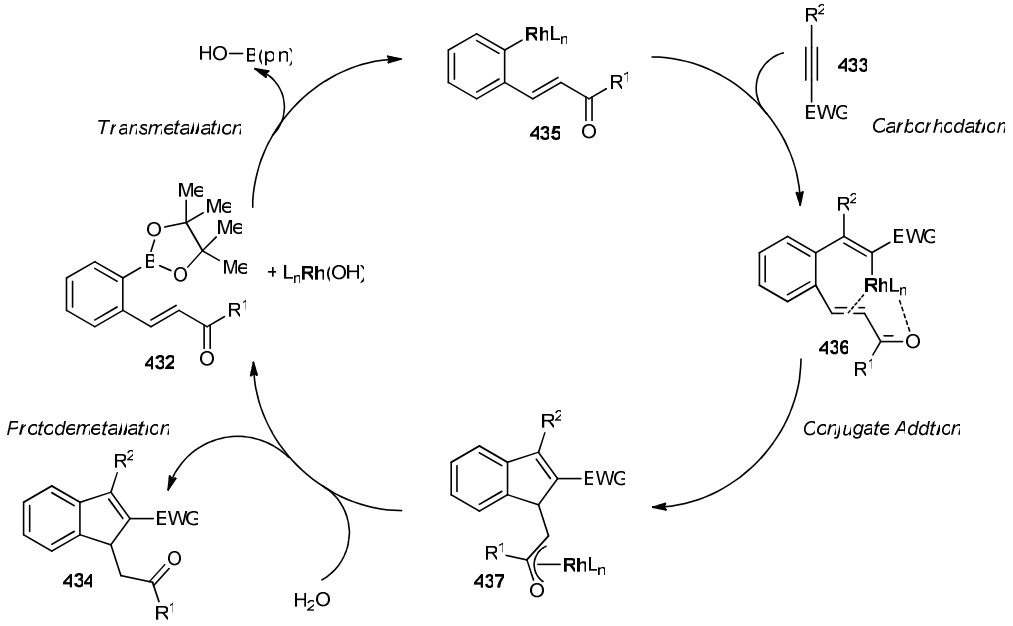
In recent years, the Lauten group has made some valuable contributions to this field of chemistry. Previously, the group had developed a synthesis of indanes employing a tandem cyclisation of *ortho*-boronate cinnamic acid derivatives with strained olefins as the coupling partners.[174] Building upon their initial results, they were able to expand the scope of the coupling partner to encompass acetylenes, thus providing access to multisubstituted indene derivatives (Scheme 5.3).[175]




**Scheme 5.3**

A full examination of the acetylenic component was undertaken and alkynes bearing heteroatoms, as well propargylic-substituted alkynes were compatible with the reaction conditions, giving the indene products in good yields and regioselectivities.

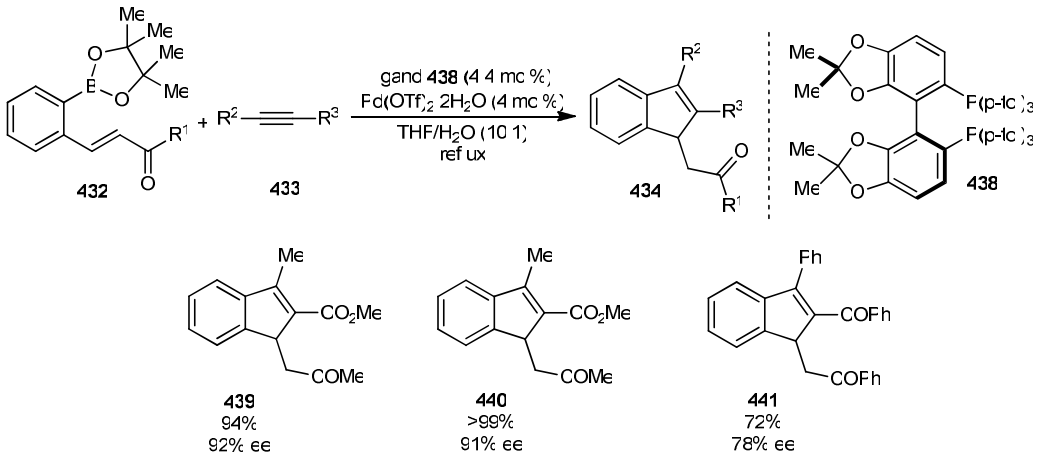
Water was used as a co-solvent in the reaction and was thought to be essential for catalytic turnover (Scheme 5.4).




**Scheme 5.4**

$L_nRh(OH)$ is believed to be the active catalyst and undergoes a transmetallation with the aryl boronate ester in the first stage of the cycle to give the organorhodium species **435**. Coordination of the alkyne, followed by carborhodation produces the vinylic rhodium intermediate **436**. Conjugate addition onto the pendant α,β-unsaturated acceptor results in the construction of the indene nucleus and the (oxa-π-allyl)rhodium **437**. Finally, protodemetallation regenerates the active catalyst and liberates the observed product.

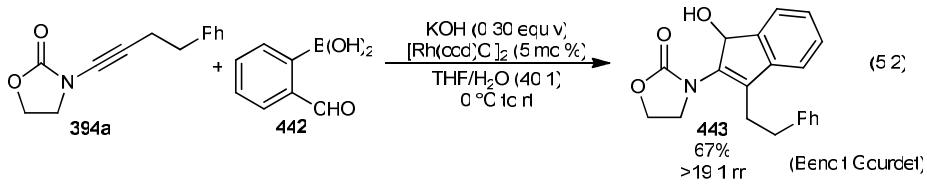
The asymmetric synthesis of indenes has been tackled by both resolution strategies[176] and chiral auxiliaries.[177] In 2009, Lu reported an enantioselective variant of Lauten's tandem cyclisation.[178] A cationic palladium-catalysed tandem reaction of *ortho*-boronate-substituted cinnamic ketones and internal alkynes yields optically active indenes and constitutes the first example of a transition metal-catalysed indene synthesis with control of the C1-stereogenic centre (Scheme 5.5).



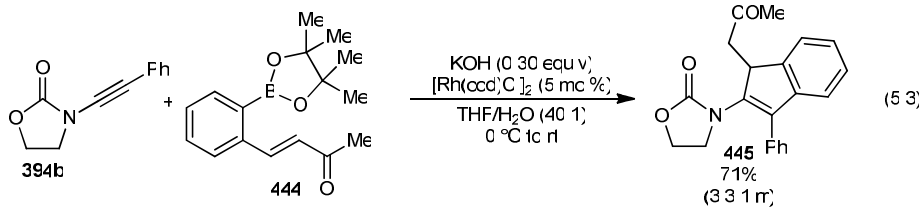

**Scheme 5.5**

A range of activated alkynes gave the desired multisubstituted indene derivatives in outstanding yields and with excellent control of the absolute stereochemistry in this elegant transformation. The proposed mechanism was analogous to that suggested by Lautens and once more a water co-solvent was necessary for the reaction to take place.

Drawing precedent from these reports, a carboannulation strategy was devised for the synthesis of indene–enamide products from ynamides and aromatic boronic acids (or boronate esters) bearing an electrophilic trap at the 2-position. After a small amount of optimisation a rhodium catalyst yielded indenol **443** from the reaction of 2-formyl-substituted aromatic boronic acid **442** (eq 5.2).




The same set of conditions furnished the carboannulation product **445** from the ynamide **394b** and the aromatic boronate ester bearing an α,β-unsaturated ketone at the *ortho*-position in good yield and regioselectivity (eq 5.3).

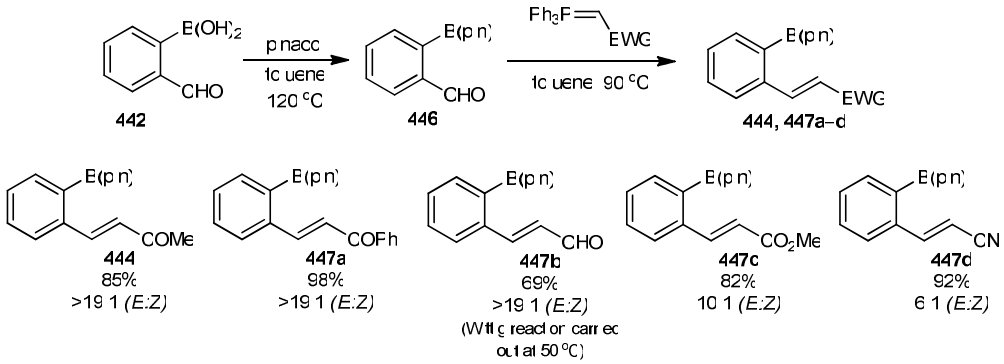


This methodology offers a one-pot synthesis of relatively complex enamide–indene structures and complements the existing literature in this area. Moreover, the use of chiral non-racemic ligands could potentially generate an enantioselective procedure to allow the synthesis of optically active indenes. The pendant enamide moiety provides an additional functional handle on the indene core that can be used in a wide range of transformations (see Chapter 3 for a full discussion) to gain access to other indene derivatives. For these reasons we embarked upon a systematic study of the scope and limitations of the transformation.

## 5.2 Results and Discussion

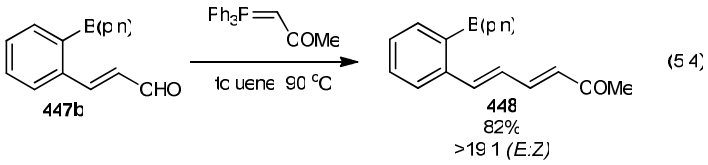
### 5.2.1 Synthesis of Starting Materials

The ynamides employed in the tandem carbometallation-conjugate addition reaction were prepared as described previously (Chapter 3). The synthesis of the aromatic boronate ester bearing a pendant electrophilic trap was straightforward (Scheme 5.6).[174a]



**Scheme 5.6**

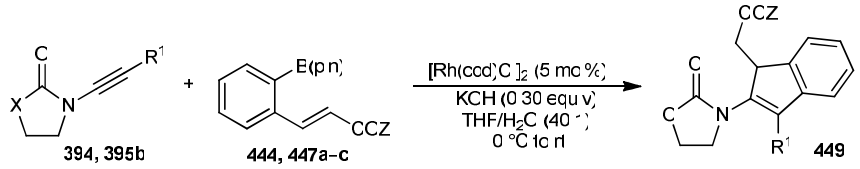
Commercially available 2-formylphenyl boronic acid was protected using pinacol to give the pinacol ester **446** in quantitative yield. Wittig reactions with different ylides provided a diverse range of α,β-unsaturated acceptors in high yields. An aromatic boronate ester bearing a pendant α,β,γ,δ-unsaturated ketone (**448**) was synthesised *via* a further Wittig reaction on the aldehyde **447b** (eq 5.4).

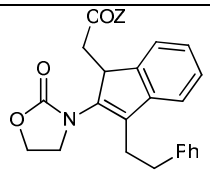
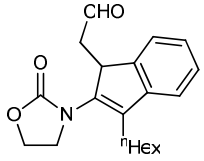
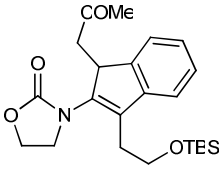
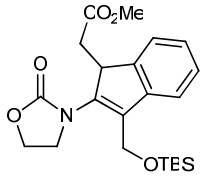
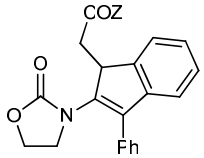
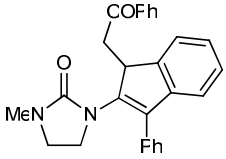
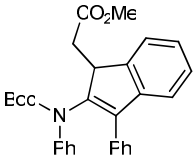


(5.4)

## 5.2.2 Rhodium-Catalysed Carbometallation–Conjugate Addition Reaction

With a set of conditions in hand, a series of ynamide substrates were investigated with a range of *ortho*-boronate substituted cinnamic acid derivatives (Table 5.1).



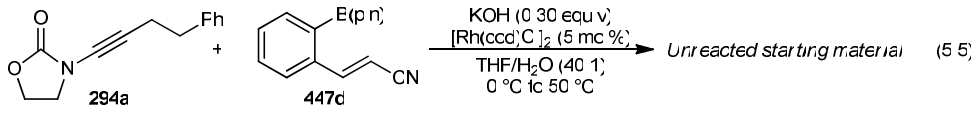

| entry | ynamide | Z | product | | rr[a] | yield (%)[b] |
|---|---|---|---|---|---|---|
| 1 | **394a** | Ph |  | **449a** | 10:1[c] | 97[d] |
| 2 | | H | | **449b** | 7:1 | 75 |
| 3 | **394c** | H |  | **449c** | 8:1 | 67 |
| 4 | **394e** | Me |  | **449d** | 11:1 | 95[d] |
| 5 | **394d** | OMe |  | **449e** | 10:1[c] | 96[d] |
| 6 | **394b** | Me |  | **445** | 3.3:1 | 71 |
| 7 | | OMe | | **449f** | 3.7:1 | 75 |
| 8 | **394i** | Ph |  | **449g** | 2:1 | 55[e] |
| 9 | **395b** | OMe |  | **449h** | 2:1 | 95[d] |

[a] Regioisomeric ratio as determined by $^1$H NMR analysis of the unpurified reaction mixtures. [b] Isolated yield of major regioisomer. [c] $^1$H NMR indicated a mixture of regioisomers, although it was not possible to obtain the rr from the spectra. As $^{13}$C NMR indicated only one regioisomer, the rr is assumed to be ≥10:1). [d] Isolated yield of both regioisomers in the same ratio as the crude. [e] 28% of the minor regioisomer was also isolated in this case.

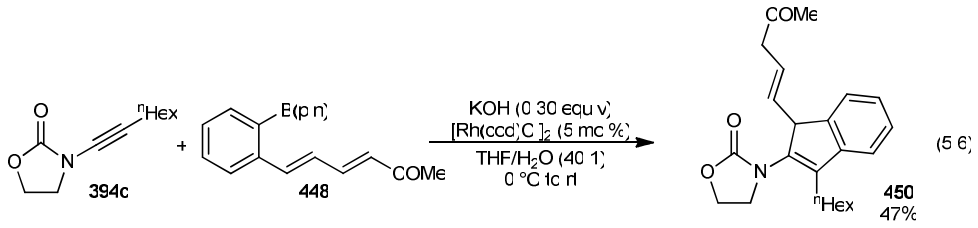
**Table 5.1**

The reactions rapidly go to completion for ynamides containing oxazolidinone and urea moieties, to give the desired indene products in good to high yields. Ynamides containing an aliphatic group at the $R^1$-position generally gave the indene products with good regioselectivities (entries 1-5), whereas phenyl-substituted ynamides resulted in poorer regioselectivities (entries 6-9). A variety of electrophilic acceptors were tolerated on the boronate coupling partner including α,β-unsaturated aromatic ketones (entries 1 and 8), α,β-unsaturated aliphatic ketones (entries 4 and 6), α,β-unsaturated aldehydes (entries 2 and 3) and α,β-unsaturated esters (entries 5, 7 and 9). The aldehyde-containing enamide products **449b** and **449c** appeared to be slightly unstable and began to decompose upon standing at room temperature for prolonged periods of time.

Attempts to use an α,β-unsaturated nitrile group as the electrophilic trap were unsuccessful and unreacted starting material was observed even after prolonged heating at 50 °C (eq 5.5).



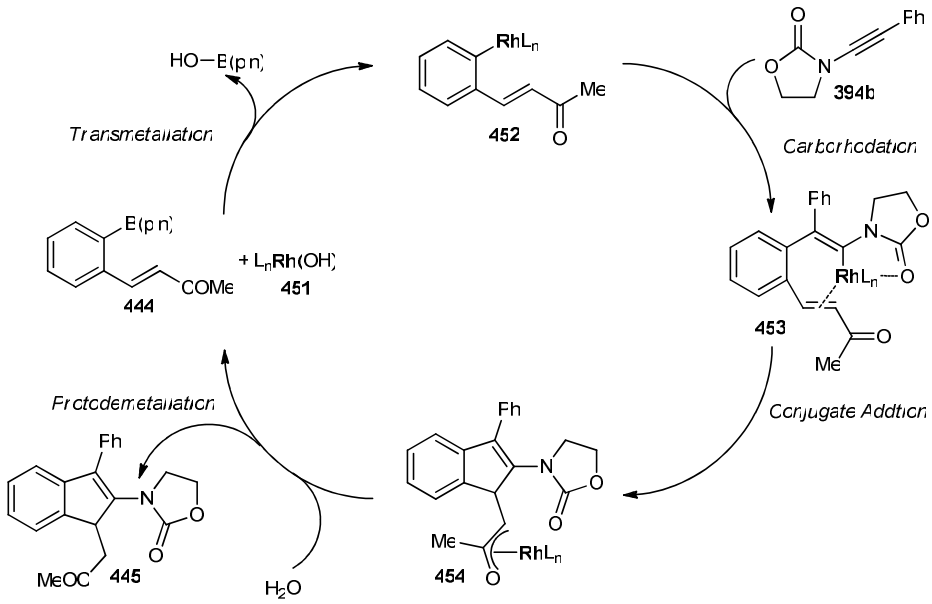

A pendant α,β,γ,δ-unsaturated ketone proved to be an effective electrophilic acceptor in the reaction and the indene product **450** was isolated in 47% yield (eq 5.6).




The crude product mixture contained a mixture of regioisomers (2.3:1 rr), although it was not possible to isolate the other components of the mixture.

### 5.2.3 Reaction Mechanism

Extrapolation from the work of Lautens[174a] and Lu[178] prompts us to propose the following mechanism (Scheme 5.7). It has been depicted using ynamide **394b** and the boronate ester **444** for illustrative purposes.




**Scheme 5.7**

The first stage of the catalytic cycle involves a transmetallation between the monohydroxo rhodium species **451** and the boronate ester to give the organorhodium species **452**. Based on our previous work on carbonyl-directed *syn*-carbometallations (Chapter 4), we assume that the carbonyl group embedded in the enamide moiety directs the carborhodation step and affords the vinylic rhodium species **453** in a regioselective fashion. The regiochemistry of the indene product **449f** was confirmed by X-ray crystallography and the rest of the indene products were assigned by analogy (Fig 5.2).

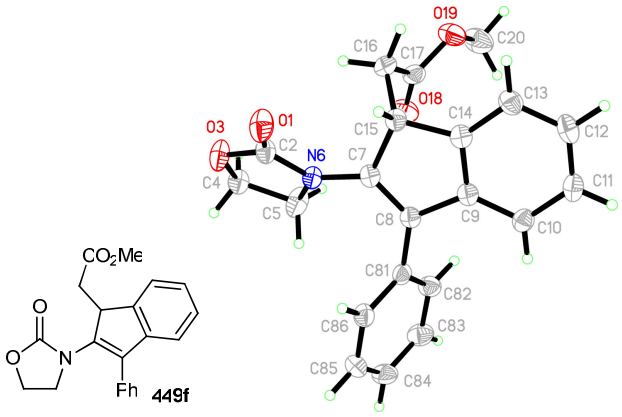
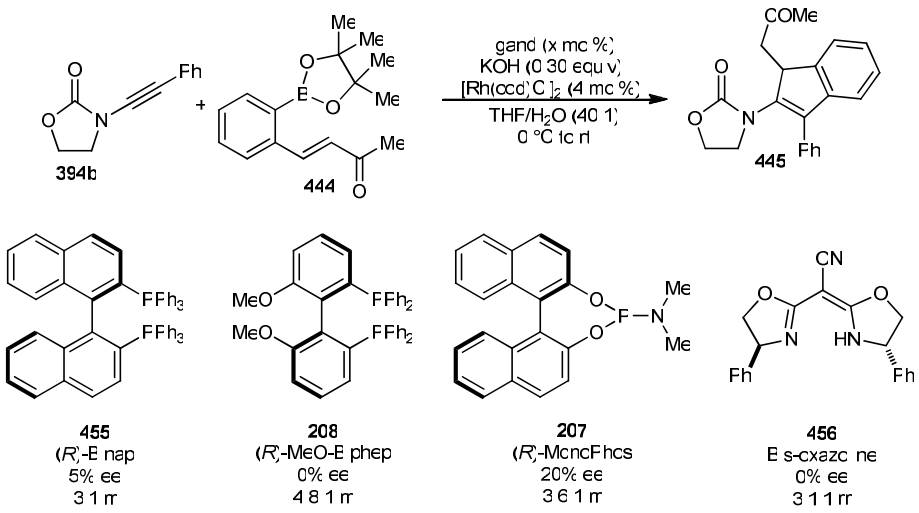



**Figure 5.2**

Conjugate addition onto the pendant α,β-unsaturated acceptor provides the (oxa-π-allyl)rhodium intermediate **454**. The observed indene product is obtained after a protodemetallation step that also regenerates the active catalyst.

### 5.2.4 Development of an Asymmetric Reaction

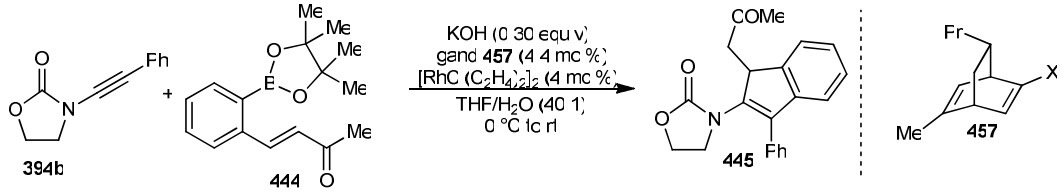
Once the scope of the reaction had been successfully explored, our endeavours were directed towards the development of an asymmetric variant, *via* the introduction of chiral non-racemic ligands into the catalytic system. Using ynamide **394b** and the boronate ester **444** as the model system, a range of common chiral ligands was investigated (Scheme 5.8).

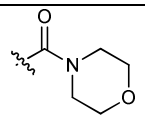
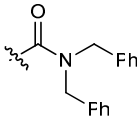



**Scheme 5.8**

In initial screenings, bidentate and monodentate phosphine ligands, as well as a bis-oxazoline ligand, were assessed for their ability to impart enantioselectivity. In the majority of cases, the ligands did not give any appreciable levels of asymmetric induction and the levels of regioselectivity obtained were approximately the same as were observed previously in the ligandless system. The best result was observed with the phosphoramidite ligand (*R*)-Monophos, which gave an ee of 20%.

Recently, Hayashi and co-workers have published a significant volume of work on chiral diene ligands for use in rhodium catalysis.[179, 180] We hoped that these types of ligands would prove amenable to our reaction conditions. A selection of diene ligands derived from (*R*)-α-phellandrene were prepared* and examined in the model system (Table 5.2).




| entry | ligand | X* | rr[a] | ee (%) |
|---|---|---|---|---|
| 1 | **457a** |  | 1:1.2 | 36 |
| 2 | **457b** |  | 1:1.1 | 22 |
| 3[b] | **457c** | $-CC_2H$ | 4.4:1 | 48 |
| 4[c] | **457d** |  | 1:1 | 71 |
| 5 | **457e** | $-CC_2Me$ | 5.3:1 | 66 |

[a] Regioisomeric ratio as determined by $^1$H NMR analysis of the unpurified reaction mixtures. [b] This reaction proceeded to 43% conversion. [c] This reaction proceeded to 36% conversion.

**Table 5.2**

* These ligands were prepared by Benoit Gourdet.

Promising levels of enantioselectivity were obtained with these chiral diene ligands. In initial experiments, the use of amide-containing diene ligands (**457a** and **457b**, entries 1 and 2) resulted in low regioselectivities and ee's. The diene ligand containing a carboxylic acid group did give marked improvements in the regioselectivity and the enantioselectivity of the reaction. However, in all of these cases the reactions were sluggish and low conversions were observed. Employing a tertiary alcohol-derived diene (**457d**, entry 4) and an ester-derived diene (**457e**, entry 5) resulted in good enantioselectivities and, in the case of the ester-containing diene we also obtained a good regioselectivity. Future work will be directed towards the further development of this asymmetric catalytic system by further investigations into these ligand classes.

## 5.3 Conclusions

Multisubstituted indene derivatives are valuable substrates in a diverse range of chemistries. Transition metal-catalysed cyclisation reactions form effective routes into these compounds. Arguably one of the most efficient methodologies employs aromatic boronate esters bearing electrophilic traps at the 2-position. Building upon these literature precedents, we have developed a rhodium-catalysed tandem carbometallation–conjugate addition approach to indenes, utilising ynamides as the acetylenic component. The reaction conditions are compatible with a range of ynamides possessing aromatic and aliphatic groups at the β-position. Furthermore, investigations revealed that α,β-unsaturated esters, ketones and aldehydes could be used as the electrophilic trap in the reaction. A plausible reaction mechanism has been proposed that involves a carbonyl-directed *syn*-carbometallation as the key step. The results of early screening for an asymmetric protocol have been disclosed and currently a maximum ee of 67% has been achieved using a diene ligand. Future work will be directed towards further optimising this procedure.

# 6.0 Experimental

**General Information**

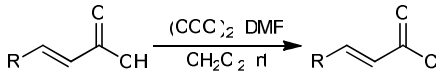
All non-aqueous reactions were carried out under a nitrogen atmosphere in oven-dried apparatus. $CH_2Cl_2$ and THF were dried and purified by passage through activated alumina columns using a solvent purification system from www.glasscontour.com 'Petrol' refers to that fraction of light petroleum ether boiling in the range 40-60 °C. Commercially available $CoCl_2$ was dried by heating under vacuum until it turned from purple to blue. All other commercially available reagents were used as received. Thin layer chromatography (TLC) was performed on Merck DF-Alufoilien $60F_{254}$ 0.2 mm precoated plates. Product spots were visualized by UV light at 254 nm, and subsequently developed using potassium permanganate or ceric ammonium molybdate solution as appropriate. Flash column chromatography was carried out using silica gel (Fisher Scientific 60Å particle size 35-70 micron) employing the method of Still and co-workers.[181] Melting points were recorded on a Gallenkamp melting point apparatus and are uncorrected. Infra-red spectra were recorded on a Jasco FT/IR-460 Plus instrument as a thin film on sodium chloride plates or as a dilute solution in $CHCl_3$. $^1H$ NMR spectra were recorded on a Bruker DPX360 (360 MHz) spectrometer or a Bruker ARX250 (250 MHz) spectrometer. Chemical shifts (δ) are quoted in parts per million (ppm) downfield of tetramethylsilane, using residual protonated solvent as internal standard ($CDCl_3$ at 7.27 ppm). Abbreviations used in the description of resonances are: s (singlet), d (doublet), t (triplet), q, (quartet), app (apparent), br (broad). Coupling constants (*J*) are quoted to the nearest 0.1 Hz. Proton-decoupled $^{13}C$ NMR spectra were recorded on a Bruker DPX360 (90.6 MHz) spectrometer or a Bruker ARX250 (62.9 MHz) spectrometer. Chemical shifts (δ) are quoted in parts per million (ppm) downfield of tetramethylsilane, using deuterated solvent as internal standard ($CDCl_3$ at 77.0 ppm). Assignments were made using the DEPT sequence with secondary pulses at 90° and 135°. High resolution mass spectra were recorded on a Finnigan MAT 900 XLT spectrometer or a Finnigan MAT 95XP spectrometer at the EPSRC National Mass Spectrometry Service Centre, University of Wales, Swansea, or on a Finnigan MAT 900 XLT spectrometer or a Kratos MS50TC spectrometer at the School of

Chemistry, University of Edinburgh. Stated calculated mass values refer to that of the *ion* (i.e. the actual species being detected), *not* that of the neutral parent compound.

# 6.1 Cobalt-Catalysed Alkylative Aldol Cyclisations

## 6.1.1 Preparation of Cyclisation Precursors

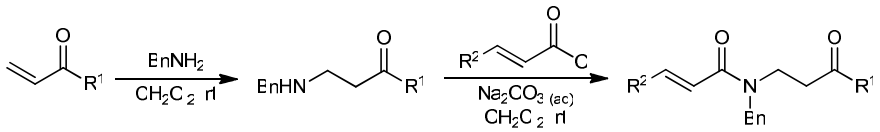
### Preparation of α,β-Unsaturated Acid Chlorides



**General Procedure A**

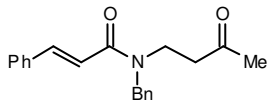
Oxalyl chloride (1.21 equiv) was added dropwise over 2 min to a solution of the appropriate α,β-unsaturated carboxylic acid (1.10 equiv) and DMF (0.25 equiv) in $CH_2Cl_2$ (0.55 M with respect to carboxylic acid) at 0 °C. The mixture was stirred at 0 °C until no more effervescence was observed (*ca.* 1 h) to give a solution of α,β-unsaturated acid chloride which was used directly in the next step.

### Preparation of Cyclisation Precursors

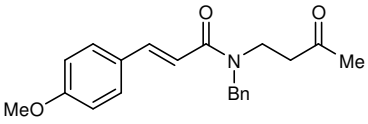


**General Procedure B**

A solution of benzylamine (1.0 equiv) and methyl vinyl ketone or ethyl vinyl ketone (1.1 equiv) in $CH_2Cl_2$ (2.5 mL/mmol of benzylamine) was stirred at 0 °C for 18 h. Saturated aqueous $Na_2CO_3$ solution (2.5 mL/mmol of benzylamine) followed by the appropriate acid chloride (neat in the case of commercially available acid chlorides, or as a solution in $CH_2Cl_2$ prepared according to General Procedure A, 1.21 equiv) were then added dropwise or portionwise and the mixture was stirred at room temperature until TLC analysis showed the reaction to be complete. The reaction was partitioned between saturated aqueous $NaHCO_3$ solution and $CH_2Cl_2$. The aqueous layer was separated and extracted with $CH_2Cl_2$ (x 3), and the combined organic layers were washed with 10% HCl solution (x 1), dried ($MgSO_4$) and concentrated *in vacuo*. Purification of the residue by column chromatography afforded the cyclisation substrate.

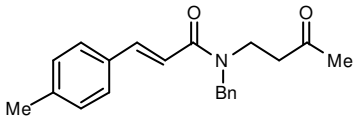


***N*-Benzyl-*N*-(3-oxobutyl)-(*E*)-3-phenylpropenamide (173)**.[59] The title compound was prepared according to General Procedure B from methyl vinyl ketone (1.98 mL, 22.0 mmol), benzylamine (2.18 mL, 20.0 mmol) and cinnamoyl chloride (4.03 g, 24.2 mmol) for a reaction time of 16 h. The product was purified by column chromatography (40% EtOAc/hexane) to give a white solid (2.78 g, 45%) as a 2:1 mixture of rotamers that displayed identical spectroscopic data to those reported previously.[59] $R_f$ = 0.20 (40% EtOAc/hexane); IR ($CHCl_3$) 3027, 1713 (C=O), 1648 (C=C), 1426, 1203, 1161, 1028, 978, 764, 700 $cm^{-1}$; $^1H$ NMR (360 MHz, $CDCl_3$) (Major rotamer) δ 7.79 (1H, d, *J* = 15.4 Hz, PhC**H**=), 7.61-7.26 (10H, m, Ar**H**), 6.86 (1H, d, *J* = 15.4 Hz, PhCH=C**H**), 4.80 (2H, s, C**H**$_2$Ph), 3.73 (2H, t, *J* = 6.7 Hz, $CH_2C\mathbf{H}_2N$), 2.90 (2H, t, *J* = 6.7 Hz, C**H**$_2CH_2N$), 2.17 (3H, s, C**H**$_3$C=O); (Minor rotamer) δ 7.85 (1H, d, *J* = 15.3 Hz, PhC**H=**), 7.61-7.26 (10H, m, Ar**H**), 7.01 (1H, d, *J* = 15.3 Hz, PhCH=C**H**), 4.76 (2H, s, C**H**$_2$Ph), 3.76 (2H, t, *J* = 7.1 Hz, $CH_2C\mathbf{H}_2N$), 2.74 (2H, t, *J* = 7.1 Hz, C**H**$_2CH_2N$), 2.13 (3H, s, C**H**$_3$C=O); $^{13}C$ NMR (62.9 MHz, $CDCl_3$) (Mixture of rotamers – not fully assigned) δ 207.4 (C), 206.0 (C), 167.0 (C), 166.4 (C), 143.5 (CH), 143.1 (CH), 137.5 (C), 137.0 (C), 135.0 (C), 129.6 (CH), 128.8 (CH), 128.6 (CH), 128.5 (CH), 127.9 (CH), 127.7 (CH), 127.6 (CH), 127.3 (CH), 126.4 (CH), 117.1 (CH), 116.9 (CH), 52.3 ($CH_2$), 49.5 ($CH_2$), 42.9 ($CH_2$), 42.6 ($CH_2$), 41.8 (2 x $CH_2$), 30.2 ($CH_3$), 30.0 ($CH_3$).



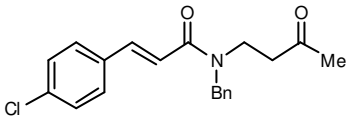
***N*-Benzyl-*N*-(3-oxobutyl)-(*E*)-3-(4-methoxyphenyl)propenamide (181)**. The title compound was prepared according to General Procedure B from methyl vinyl ketone (1.98 mL, 22.0 mmol), benzylamine (2.18 mL, 20.0 mmol) and the acid chloride (prepared according General Procedure A) derived from 4-methoxycinnamic acid (4.30 g, 24.2 mmol) for a reaction time of 20 h. The product was purified by column chromatography (55% EtOAc/petrol) to give a yellow solid (3.79 g, 55%) as a 2:1 mixture of rotamers. $R_f$ = 0.10 (50% EtOAc/hexane); m.p. 67-70 °C; IR ($CHCl_3$) 2937, 1714 (C=O), 1645 (C=C), 1603, 1512, 1173, 1028, 908, 736 $cm^{-1}$; $^1H$ NMR (360 MHz, $CDCl_3$) (Major rotamer) δ 7.71 (1H, d, *J* = 15.3 Hz, PhC**H**=), 7.51-7.22 (7H, m, Ar**H**), 6.92-6.80 (2H, m, Ar**H**),

6.69 (1H, d, *J* = 15.3 Hz, PhCH=C**H**), 4.74 (2H, s, C**H**$_2$Ph), 3.80 (3H, s, OC**H**$_3$), 3.70-3.66 (2H, m, CH$_2$C**H**$_2$N), 2.85 (2H, t, *J* = 6.6 Hz, C**H**$_2$CH$_2$N), 2.13 (3H, s, C**H**$_3$C=O); (Minor rotamer) δ 7.76 (1H, d, *J* = 15.6 Hz, PhC**H=**), 7.51-7.22 (7H, m, Ar**H**), 6.92-6.80 (3H, m, Ar**H** and PhCH=C**H**), 4.71 (2H, s, C**H**$_2$Ph), 3.83 (3H, s, OC**H**$_3$), 3.70-3.66 (2H, m, CH$_2$C**H**$_2$N), 2.69 (2H, t, *J* = 6.4 Hz, C**H**$_2$CH$_2$N), 2.08 (3H, s, C**H**$_3$C=O); $^{13}$C NMR (62.9 MHz, $CDCl_3$) (Mixture of rotamers – not fully assigned) δ 207.5 (C), 167.4 (C), 160.9 (C), 143.3 (CH), 142.9 (CH), 137.2 (C), 129.4 (CH), 128.8 (CH), 128.6 (CH), 127.8 (CH), 126.5 (CH), 114.7 (CH), 114.1 (CH), 55.3 ($CH_3$), 52.3 ($CH_2$), 42.6 ($CH_2$), 42.0 ($CH_2$), 30.0 ($CH_3$); HRMS (EI) Exact mass calcd for $C_{21}H_{23}NO_3$ $[M]^+$: 337.1672, found: 337.1667.

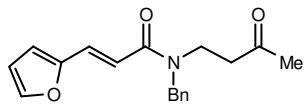



***N*-Benzyl-*N*-(2-oxobutyl)-3-(4-methylphenyl)propenamide (182)**. The title compound was prepared according to General Procedure B from methyl vinyl ketone (1.98 mL, 22.0 mmol), benzylamine (2.18 mL, 20.0 mmol) and the acid chloride (prepared according General Procedure A) derived from (*E*)-3-(4-methylphenyl)acrylic acid (3.97 g, 24.2 mmol) for a reaction time of 20 h. The product was purified by column chromatography (40% EtOAc/petrol) to give a yellow oil (which solidified to a cream solid on standing) (2.46 g, 38%) as a 2:1 mixture of rotamers. $R_f$ = 0.15 (40% EtOAc/petrol); m.p. 99-102 °C; IR ($CHCl_3$) 3030, 1714 (C=O), 1646 (C=C), 1602, 1444, 1204, 907, 731, 650 cm$^{-1}$; $^1$H NMR (360 MHz, $CDCl_3$) (Major rotamer) δ 7.73 (1H, d, *J* = 15.3 Hz, PhC**H**=), 7.47-7.13 (9H, m, Ar**H**), 6.78 (1H, d, *J* = 15.3 Hz, PhCH=C**H**), 4.76 (2H, s, C**H**$_2$Ph), 3.70-3.67 (2H, m, CH$_2$C**H**$_2$N), 2.86 (2H, t, *J* = 6.7 Hz, C**H**$_2$CH$_2$N), 2.35 (3H, s, C**H**$_3$Ar), 2.14 (3H, s, C**H**$_3$C=O); (Minor rotamer) δ 7.79 (1H, d, *J* = 15.5 Hz, PhC**H=**), 7.47-7.13 (9H, m, Ar**H**), 7.73 (1H, d, *J* = 15.5 Hz, PhCH=C**H**), 4.72 (2H, s, C**H**$_2$Ph), 3.70-3.67 (2H, m, CH$_2$C**H**$_2$N), 2.70 (2H, t, *J* = 6.7 Hz, C**H**$_2$CH$_2$N), 2.38 (3H, s, C**H**$_3$Ar), 2.10 (3H, s, C**H**$_3$C=O); $^{13}$C NMR (62.9 MHz, $CDCl_3$) (Mixture of rotamers – not fully assigned) δ 207.5 (C), 167.3 (C), 143.3 (CH), 140.0 (C), 137.2 (C), 132.4 (C), 129.5 (CH), 128.9 (CH), 128.6 (CH), 128.1 (CH), 127.8 (CH), 127.6 (CH), 126.5 (CH), 116.2 (CH), 52.4 ($CH_2$), 42.6 ($CH_2$), 42.0 ($CH_2$), 30.1 ($CH_3$), 21.3

(2 x $CH_3$); HRMS (EI) Exact mass calcd for $C_{21}H_{23}NO_2$ $[M]^+$: 321.1723, found: 321.1720.

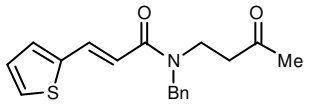


***N*-Benzyl-*N*-(2-oxobutyl)-3-(4-chlorophenyl)propenamide (183)**. The title compound was prepared according to General Procedure B from methyl vinyl ketone (1.98 mL, 22.0 mmol), benzylamine (2.18 mL, 20.0 mmol) and the acid chloride (prepared according General Procedure A) derived from (*E*)-3-(4-chlorophenyl)acrylic acid (4.42 g, 24.2 mmol) for a reaction time of 20 h. The product was purified by column chromatography (40% EtOAc/petrol) to give an off-white solid (2.53 g, 37%) as a 2:1 mixture of rotamers. $R_f$ = 0.18 (40% EtOAc/petrol); m.p. 91-93 °C; IR ($CHCl_3$) 3032, 1714 (C=O), 1649 (C=C), 1604, 1492, 1092, 908, 729, 650 $cm^{-1}$; $^1H$ NMR (360 MHz, $CDCl_3$) (Major rotamer) δ 7.68 (1H, d, *J* = 15.4 Hz, PhC**H**=), 7.51-7.21 (9H, m, Ar**H**), 6.78 (1H, d, *J* = 15.4 Hz, PhCH=C**H**), 4.75 (2H, s, C$\mathbf{H}_2$Ph), 3.73-3.66 (2H, m, $CH_2$C$\mathbf{H}_2$N), 2.85 (2H, t, *J* = 6.6 Hz, C$\mathbf{H}_2$$CH_2$N), 2.13 (3H, s, C$\mathbf{H}_3$C=O); (Minor rotamer) δ 7.73 (1H, d, *J* = 15. 6 Hz, PhC**H**=), 7.51-7.21 (9H, m, Ar**H**), 6.97 (1H, d, *J* = 15.6 Hz, PhCH=C**H**), 4.71 (2H, s, C$\mathbf{H}_2$Ph), 3.76-3.66 (2H, m, $CH_2$C$\mathbf{H}_2$N), 2.68 (2H, t, *J* = 6.7 Hz, C$\mathbf{H}_2$$CH_2$N), 2.08 (3H, s, C$\mathbf{H}_3$C=O); $^{13}C$ NMR (62.9 MHz, $CDCl_3$) (Mixture of rotamers – not fully assigned) δ 207.3 (C), 206.0 (C), 166.8 (C), 166.3 (C), 147.1 (C), 142.1 (CH), 141.8 (CH), 137.0 (C), 135.4 (C), 133.6 (C), 133.5 (C), 129.6 (CH), 129.3 (CH), 128.9 (CH), 128.6 (CH), 128.0 (CH), 127.7 (CH), 127.4 (CH), 126.4 (CH), 117.8 (CH), 117.6 (CH), 114.8 (CH), 52.4 ($CH_2$), 49.6 ($CH_2$), 42.8 ($CH_2$), 42.7 ($CH_2$), 41.9 ($CH_2$), 30.3 ($CH_3$), 30.0 ($CH_3$); HRMS (EI) Exact mass calcd for $C_{20}H_{20}ClNO_2$ $[M]^+$: 341.1177, found: 341.1171.



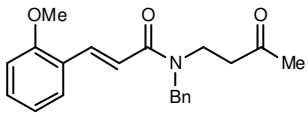
***N*-Benzyl-*N*-(3-oxobutyl)-(*E*)-3-furan-2-ylpropenamide (184)**.[59] The title compound was prepared according to the General Procedure B from methyl vinyl ketone (1.98 mL, 22.0 mmol), benzylamine (2.18 mL, 20.0 mmol) and the acid chloride (prepared according General Procedure A) derived from (2-furyl)acrylic acid (3.34 g, 24.2 mmol) for a reaction time of 16 h. The product was purified by column chromatography (40% - 60% EtOAc/petrol) to

give an orange-brown oil (2.49 g, 42%) as a 2:1 mixture of rotamers that displayed identical spectroscopic data to those reported previously.[59] $R_f$ = 0.17 (40% EtOAc/hexane); IR (film) 2923, 1713 (C=O), 1650 (C=C), 1423, 1214, 1161, 1016, 815, 732, 698 $cm^{-1}$; $^1H$ NMR (360 MHz, $CDCl_3$) (Major rotamer) δ 7.55 (1H, d, *J* = 15.1 Hz, C**H**=CHC=O), 7.50-7.24 (6H, m, Ar**H** and C**H**), 6.78 (1H, d, *J* = 15.1 Hz, CH=C**H**C=O), 6.58 (1H, bs, C**H**), 6.46-6.45 (1H, m, C**H**), 4.77 (2H, s, C**H**$_2$Ph), 3.69 (2H, t, *J* = 6.4 Hz, $CH_2C\mathbf{H}_2N$), 2.87 (2H, t, *J* = 6.4 Hz, C**H**$_2CH_2N$), 2.15 (3H, s, C**H**$_3$C=O); (Minor rotamer) δ 7.61 (1H, d, *J* = 15.2 Hz, C**H**=CHC=O), 7.50-7.24 (6H, m, Ar**H** and C**H**), 6.84 (1H, d, *J* = 15.2 Hz, CH=C**H**C=O), 6.62-6.58 (1H, m, C**H**), 6.50-6.49 (1H, m, C**H**), 4.74 (2H, s, C**H**$_2$Ar), 3.71 (2H, t, *J* = 6.9 Hz, $CH_2C\mathbf{H}_2N$), 2.74 (2H, t, *J* = 6.9 Hz, C**H**$_2CH_2N$), 2.13 (3H, s, C**H**$_3$C=O); $^{13}C$ NMR (62.9 MHz, $CDCl_3$) (Mixture of rotamers – not fully assigned) δ 207.5 (C), 206.1 (C), 166.9 (C), 166.3 (C), 151.5 (C), 143.9 (CH), 137.6 (C), 137.1 (C), 130.3 (CH), 129.9 (CH), 128.8 (CH), 128.6 (CH), 128.0 (CH), 127.6 (CH), 127.4 (CH), 126.6 (CH), 114.6 (CH), 114.3 (CH), 114.2 (CH), 114.0 (CH), 112.1 (CH) 52.2 ($CH_2$), 49.6 ($CH_2$), 43.1 ($CH_2$), 42.5 ($CH_2$), 41.9 ($CH_2$), 30.2 ($CH_3$), 30.0 ($CH_3$).

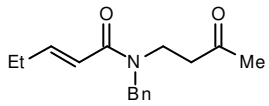



***N*-Benzyl-*N*-(3-oxobutyl)-(*E*)-3-thiophen-2-ylpropenamide (185)**. The title compound was prepared according to General Procedure B from methyl vinyl ketone (0.48 mL, 5.3 mmol), benzylamine (0.52 mL, 4.8 mmol) and the acid chloride (prepared according General Procedure A) derived from (*E*)- 3-thiophen-2-ylacrylic acid (4.30 g, 24.2 mmol) for a reaction time of 16 h. The product was purified by column chromatography (10% acetone/petrol→25% acetone/petrol) to give a yellow oil (440 mg, 30%) as a 2:1 mixture of rotamers. $R_f$ = 0.21 (40% EtOAc/hexane); IR (film) 1717 (C=O), 1642 (C=C), 1606, 1455, 1371, 1265, 1207, 1082, 905, 737 $cm^{-1}$; $^1H$ NMR (360 MHz, $CDCl_3$) (Major rotamer) δ 7.85 (1H, d, *J* = 15.0 Hz, ArC**H**=), 7.38-7.16 (7H, m, Ar**H**), 7.06-6.99 (1H, m, Ar**H**), 6.63 (1H, *J* = 15.0 Hz, ArCH=C**H**), 4.72 (2H, s, C**H**$_2$Ph), 3.67 (3H, t, *J* = 6.5 Hz, $CH_2C\mathbf{H}_2N$), 2.83 (2H, t, *J* = 6.7 Hz, C**H**$_2CH_2N$), 2.13 (3H, s, C**H**$_3$C=O); (Minor rotamer) δ 7.91 (1H, d, *J* = 15.1 Hz, ArC**H=**), 7.38-7.16 (7H, m, Ar**H**), 7.06-6.99 (1H, m, Ar**H**), 6.73 (1H, d, *J* = 15.1 Hz, ArCH=C**H**), 4.72 (2H, s, C**H**$_2$Ph), 3.67 (2H, t, *J* = 6.5 Hz, $CH_2C\mathbf{H}_2N$), 2.68

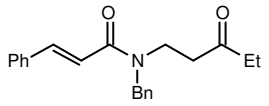
(2H, t, $J$ = 6.9 Hz, C**H**$_2$CH$_2$N), 2.09 (3H, s, C**H**$_3$C=O); $^{13}$C NMR (62.9 MHz, $CDCl_3$) (Mixture of rotamers – not fully assigned) δ 207.5 (C), 166.9 (C), 166.8 (C), 140.3 (C), 137.6 (C), 137.1 (C), 136.3 (CH), 135.9 (CH), 130.3 (CH), 128.9 (C), 128.7 (CH), 128.6 (CH), 128.0 (CH), 127.7 (CH), 127.4 (CH), 126.6 (CH), 116.0 (CH), 115.7 (CH), 52.4 ($CH_2$), 49.6 ($CH_2$), 43.1 ($CH_2$), 42.6 ($CH_2$), 42.0 ($CH_2$), 41.9 ($CH_2$), 41.8 ($CH_2$), 30.3 ($CH_3$), 30.1 ($CH_3$); HRMS (EI) Exact mass calcd for $C_{18}H_{19}NO_2S$ $[M]^+$: 313.1131, found: 313.1131.




***N*-Benzyl-*N*-(3-oxobutyl)-(*E*)-3-(2-methoxyphenyl)propenamide (186)**. The title compound was prepared according to General Procedure B from methyl vinyl ketone (1.98 mL, 22.0 mmol), benzylamine (2.18 mL, 20 mmol) and the acid chloride (prepared according General Procedure A) derived from 2-methoxycinnamic acid (4.30 g, 24.2 mmol) for a reaction time of 5 h. The product was purified by column chromatography (30% EtOAc/hexane) to give a yellow oil (3.19 g, 47%) as a 2:1 mixture of rotamers. $R_f$ = 0.32 (50% EtOAc/hexane); IR (film) 2925, 1718 (C=O), 1643 (C=C), 1599, 1461, 1369, 1254, 1165, 909, 736 cm$^{-1}$; $^1$H NMR (360 MHz, $CDCl_3$) (Major rotamer) δ 7.99 (1H, d, $J$ = 15.6 Hz, ArC**H**=), 7.38-7.23 (7H, m, Ar**H**), 6.97 (1H, d, $J$ = 15.6 Hz, ArCH=C**H**), 6.92-6.85 (2H, m, Ar**H**), 4.74 (2H, s, C**H**$_2$Ph), 3.77 (3H, s, OC**H**$_3$), 3.69 (2H, t, $J$ = 6.8 Hz, CH$_2$C**H**$_2$N), 2.85 (2H, t, $J$ = 6.7 Hz, C**H**$_2$CH$_2$N), 2.12 (3H, s, C**H**$_3$C=O); (Minor rotamer) δ 8.03 (1H, d, $J$ = 15.5 Hz, ArC**H=**), 7.38-7.23 (7H, m, Ar**H**), 7.10 (1H, d, $J$ = 15.5 Hz, ArCH=C**H**), 6.92-6.85 (2H, m, Ar**H**), 4.72 (2H, s, C**H**$_2$Ph), 3.87 (3H, s, OC**H**$_3$), 3.69 (2H, t, $J$ = 6.8Hz, CH$_2$C**H**$_2$N), 2.69 (2H, t, $J$ = 6.9 Hz, C**H**$_2$CH$_2$N), 2.07 (3H, s, C**H**$_3$C=O); $^{13}$C NMR (62.9 MHz, $CDCl_3$) (Mixture of rotamers – not fully assigned) δ 207.5 (C), 206.1 (C), 167.7 (C), 167.0 (C), 158.2 (C), 158.1 (C), 139.2 (CH), 138.7 (CH), 137.3 (C), 130.6 (CH), 129.4 (CH), 129.1 (CH), 128.7 (CH), 128.5 (CH), 128.0 (CH), 127.4 (CH), 127.2 (CH), 126.4 (CH), 124.0 (C), 120.4 (CH), 118.2 (CH), 117.8 (CH), 111.0 (CH), 55.2 ($CH_3$), 52.3 ($CH_2$), 49.5 ($CH_2$), 42.9 ($CH_2$), 42.6 ($CH_2$), 41.9 ($CH_2$), 30.2 ($CH_3$), 30.0 ($CH_3$); HRMS (ES) Exact mass calcd for $C_{21}H_{24}NO_3$ $[M+H]^+$: 338.1757, found: 338.1759.

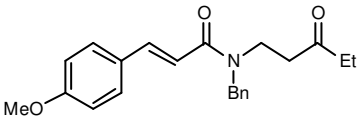



***N*-Benzyl-*N*-(3-oxobutyl)-(*E*)-3-pent-2-enamide (187)**. The title compound was prepared according to General Procedure B from methyl vinyl ketone (1.98 mL, 22.0 mmol), benzylamine (2.18 mL, 20 mmol) and the acid chloride (prepared according General Procedure A) derived from (*E*)-pent-2-enoic acid (2.42 g, 24.2 mmol) for a reaction time of 4 h. The product was purified by column chromatography (55% EtOAc/hexane) to give a pale yellow oil (2.55 g, 49%) as a 2:1 mixture of rotamers. $R_f$ = 0.11 (50% EtOAc/hexane); IR (film) 3410, 1717 (C=O), 1650 (C=C), 1606, 1442, 1375, 1158, 976, 910, 732 $cm^{-1}$; $^1$H NMR (360 MHz, $CDCl_3$) (Major rotamer) δ 7.34-7.14 (5H, m, Ar**H**), 7.06-6.93 (1H, m, $CH_2C$**H**=), 6.16 (1H, d, *J* = 15.0 Hz, $CH_2CH$=C**H**), 4.63 (2H, s, C**H**$_2$Ph), 3.58 (2H, t, *J* = 6.9 Hz, $CH_2C$**H**$_2$N), 2.78 (2H, t, *J* = 6.7 Hz, C**H**$_2CH_2$N), 2.25-2.11 (2H, m, C**H**$_2$CH=), 2.08 (3H, s, C**H**$_3$C=O), 0.98 (3H, t, *J* = 7.4 Hz, C**H**$_3CH_2$); (Minor rotamer) δ 7.34-7.14 (5H, m, Ar**H**), 7.06-6.93 (1H, m, $CH_2C$**H**=), 6.25 (1H, d, *J* = 14.9 Hz, $CH_2CH$=C**H**) 4.63 (2H, s, C**H**$_2$Ph), 3.58 (2H, t, *J* = 6.9 Hz, $CH_2C$**H**$_2$N), 2.62 (2H, t, *J* = 6.9 Hz, C**H**$_2CH_2$N), 2.05 (3H, s, C**H**$_3$C=O), 1.06 (3H, t, *J* = 7.5 Hz, C**H**$_3CH_2$); $^{13}$C NMR (62.9 MHz, $CDCl_3$) (Mixture of rotamers – not fully assigned) δ 207.5 (C), 206.1 (C), 167.3 (C), 166.6 (C), 149.1 (CH), 148.6 (CH), 137.6 (C), 137.1 (C), 128.7 (CH), 128.5 (CH), 127.9 (CH), 127.4 (CH), 127.3 (CH), 127.2 (CH), 126.4 (CH), 119.1 (CH), 118.8 (CH), 52.1 ($CH_2$), 49.2 ($CH_2$), 42.7 ($CH_2$), 42.2 ($CH_2$), 41.8 ($CH_2$), 30.2 ($CH_3$), 29.9 ($CH_3$), 25.4 ($CH_2$), 12.4 ($CH_3$); HRMS (ES) Exact mass calcd for $C_{16}H_{22}NO_2$ $[M+H]^+$: 260.1645, found: 260.1647.




***N*-Benzyl-*N*-(3-oxopentyl)-(*E*)-3-phenylpropenamide (188)**. The title compound was prepared according to General Procedure B from ethyl vinyl ketone (1.09 mL, 11.0 mmol), benzylamine (1.09 mL, 10 mmol) and cinnamoyl chloride (2.02 g, 12.1 mmol) for a reaction time of 17 h. The product was purified by column chromatography (40% EtOAc/hexane→18% acetone/petrol) to give a yellow solid (0.747 g, 23%) as a 2:1 mixture of rotamers. $R_f$ = 0.34 (40% EtOAc/hexane); m.p. 68-70 °C; IR ($CHCl_3$) 3155, 1712 (C=O), 1648 (C=C), 1602, 1452, 1377, 1206, 906, 735, 651 $cm^{-1}$; $^1$H NMR (360 MHz, $CDCl_3$) (Major rotamer) δ 7.75 (1H, d, *J* = 15.4 Hz, PhC**H**=), 7.57-7.23 (10H, m, Ar**H**), 6.83 (1H, d, *J* = 15.4 Hz, PhCH=C**H**), 4.77 (2H, s, C**H**$_2$Ph), 3.74-3.68 (2H, m,

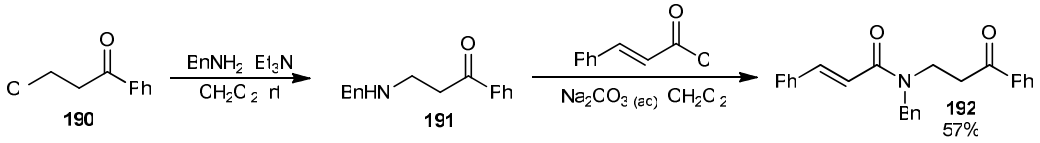
$CH_2CH_2N$), 2.84 (2H, t, *J* = 6.7 Hz, $CH_2CH_2N$), 2.42 (2H, q, *J* = 7.4 Hz, $CH_3CH_2C{=}O$), 1.04 (3H, t, *J* = 6.9 Hz, $CH_3CH_2C{=}O$); (Minor rotamer) δ 7.81 (1H, d, *J* = 15.5 Hz, PhC**H=**), 7.57-7.23 (10H, m, Ar**H**), 6.97 (1H, d, *J* = 15.2 Hz, PhCH=C**H**), 4.72 (2H, s, $CH_2Ph$), 3.74-3.68 (2H, m, $CH_2CH_2N$), 2.66 (2H, t, *J* = 7.0 Hz, $CH_2CH_2N$), 2.34 (2H, q, *J* = 7.2 Hz, $CH_3CH_2C{=}O$), 1.06-1.00 (3H, m, $CH_3CH_2C{=}O$); $^{13}C$ NMR (62.9 MHz, $CDCl_3$) (Mixture of rotamers – not fully assigned) δ 210.2 (C), 209.0 (C), 167.1 (C), 143.6 (CH), 143.2 (CH), 137.2 (C), 135.1 (C), 129.6 (CH), 128.9 (CH), 128.7 (CH), 128. 1 (CH), 127.8 (CH), 127.6 (CH), 126.5 (CH), 117.3 (CH), 52.4 ($CH_2$), 49.6 ($CH_2$), 42.8 ($CH_2$), 42.1 ($CH_2$), 41.7 ($CH_2$), 40.6 ($CH_2$), 36.4 ($CH_2$), 36.1 ($CH_2$), 7.6 ($CH_3$), 7.5 ($CH_3$); HRMS (EI) Exact mass calcd for $C_{21}H_{23}NO_2$ $[M]^+$: 321.7123, found: 321.1725.




***N*-Benzyl-*N*-(3-oxopentyl)-(*E*)-3-(4-methoxy)phenylpropenamide (189)**. The title compound was prepared according to General Procedure B from ethyl vinyl ketone (2.18 mL, 22.0 mmol), benzylamine (2.18 mL, 20 mmol) and the acid chloride (prepared according General Procedure A) derived from 4-methoxycinnamic acid (4.30 g, 24.2 mmol) for a reaction time of 20 h. The product was purified by column chromatography (45% EtOAc/hexane→25% acetone/petrol) to give a white solid (2.36 g, 34%) as a 2:1 mixture of rotamers. $R_f$ = 0.23 (40% EtOAc/hexane); m.p. 71-73 °C; IR ($CHCl_3$) 3033, 1712 (C=O), 1645 (C=C), 1512, 1254, 1173, 1033, 902, 718, 650 $cm^{-1}$; $^1H$ NMR (360 MHz, $CDCl_3$) (Major rotamer) δ 7.70 (1H, d, *J* = 15.3 Hz, ArC**H=**), 7.51-7.21 (7H, m, Ar**H**), 6.91-6.80 (2H, m, Ar**H**), 6.69 (1H, d, *J* = 15.3 Hz, ArCH=C**H**), 4.75 (2H, s, $CH_2Ph$), 3.79 (3H, s, $OCH_3$), 3.73-3.66 (2H, m, $CH_2CH_2N$), 2.82 (2H, t, *J* = 6.6 Hz, $CH_2CH_2N$), 2.43-2.32 (2H, m, $CH_3CH_2C{=}O$), 1.02 (3H, t, *J* = 7.3 Hz, $CH_3CH_2C{=}O$); (Minor rotamer) δ 7.76 (1H, d, *J* = 15.6 Hz, ArC**H=**), 7.51-7.21 (7H, m, Ar**H**), 6.91-6.80 (3H, m, Ar**H** and ArCH=C**H**), 4.71 (2H, s, $CH_2Ph$), 3.82 (3H, s, $OCH_3$), 3.73-3.66 (2H, m, $CH_2CH_2N$), 2.65 (2H, t, *J* = 6.6 Hz, $CH_2CH_2N$), 2.43-2.32 (2H, m, $CH_3CH_2C{=}O$), 1.04-0.98 (3H, m, $CH_3CH_2C{=}O$); $^{13}C$ NMR (62.9 MHz, $CDCl_3$) (Mixture of rotamers – not fully assigned) δ 210.2 (C), 209.0 (C), 167.3 (C), 166.7 (C), 160.8 (C), 143.2 (CH), 142.8 (CH), 137.8 (C), 137.3 (C), 129.3 (CH), 128.8

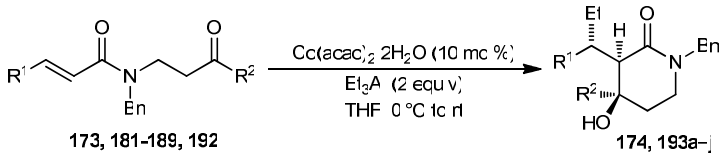
(CH), 128.5 (CH), 128.0 (CH), 127.8 (C), 127.5 (CH), 127.3 (CH), 127.3 (CH), 126.4 (CH), 114.7 (CH), 114.1 (CH), 55.2 ($CH_3$), 52.3 ($CH_3$), 49.5 ($CH_2$), 42.7 ($CH_2$), 42.0 ($CH_2$), 41.7 ($CH_2$), 41.5 ($CH_2$), 40.6 ($CH_2$), 36.4 ($CH_2$), 36.0 ($CH_2$), 7.5 ($CH_3$); HRMS (EI) Exact mass calcd for $C_{22}H_{25}NO_3$ $[M]^+$: 351.1829, found: 351.1825.

***N*-Benzyl-*N*-(3-oxo-3-phenylpropyl)-(*E*)-3-phenylpropenamide (192).**




The title compound was prepared by Dr Pekka Joensuu.[61]

## 6.1.2 Cobalt-Catalyzed Alkylative Aldol Cyclisations




**Using $Et_3Al$: General Procedure C**

A solution of the substrate (1 equiv) and $Co(acac)_2{\cdot}2H_2O$ (0.10 equiv) in THF (1.5 mL) was stirred at room temperature for 15 min. The mixture was cooled to 0 °C and stirred for a further 15 min. $Et_3Al$ (1 M solution in hexane, 2 equiv) was then added rapidly in one portion. The reaction was stirred at 0 °C for 1 h and then at room temperature until the reaction had stopped progressing as observed by TLC analysis. Workup was carried out according to one of the procedures described below.

**Using $Me_3Al$: General Procedure D**

A solution of the substrate (0.20 mmol) and $Co(acac)_2{\cdot}2H_2O$ (2.6 mg, 0.01 mmol) in THF (1.5 mL) was stirred at room temperature for 15 min. The mixture was cooled to 0 °C and stirred for a further 15 min. $Me_3Al$ (2 M solution in hexane, 0.20 mL, 0.40 mmol) was then added rapidly in one portion. The reaction was stirred at 0 °C for 1 h and then at room temperature until the reaction had stopped progressing as

observed by TLC analysis. Workup was carried out according to one of the procedures described below.

**Using $^{n}Pr_3Al$: General Procedure E**

A solution of the substrate (0.20 mmol) and $Co(acac)_2 \cdot 2H_2O$ (2.6 mg, 0.01 mmol) in THF (1.5 mL) was stirred at room temperature for 15 min. The mixture was cooled to 0 °C and stirred for a further 15 min. $^{n}Pr_3Al$ (0.7 M solution in hexane, 0.57 mL, 0.40 mmol) was then added rapidly in one portion. The reaction was stirred at 0 °C for 1 h and then at room temperature until the reaction had stopped progressing as observed by TLC analysis. Workup was carried out according to one of the procedures described below.

**Using $^{n}Hex_3Al$ : General Procedure F**

A solution of the substrate (0.20 mmol) and $Co(acac)_2 \cdot 2H_2O$ (2.6 mg, 0.01 mmol) in THF (1.5 mL) was stirred at room temperature for 15 min. The mixture was cooled to 0 °C and stirred for a further 15 min. $^{n}Hex_3Al$ (0.4 M solution in hexane, 1 mL, 0.40 mmol) was then added quickly. The reaction was stirred at 0 °C for 1 h and then at room temperature until the reaction had stopped progressing as observed by TLC analysis. Workup was carried out according to one of the procedures described below.

**Workup A**

Saturated aqueous Rochelle's salt (potassium sodium tartrate) solution (2 mL) was added carefully and the resulting mixture was stirred vigorously for 30 min. The mixture was then further diluted with Rochelle's salt solution (20 mL) and the aqueous layer was separated and extracted with $CH_2Cl_2$ (3 x 15 mL). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. Purification of the residue by column chromatography afforded the cyclised product.

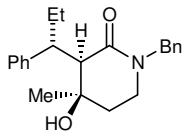
**Workup B**

10% HCl solution (1 mL) was added carefully and the resulting mixtures was stirred vigorously for 30 min. The mixture was then further diluted with a 1:1 solution of

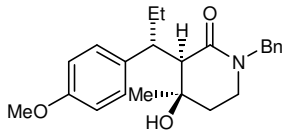
saturated $NH_4Cl$ solution and 10% HCl solution (10 mL). The aqueous layer was separated and extracted with $CH_2Cl_2$ (3 x 15 mL). The combined organic layers were dried ($MgSO_4$) and the filtrate was concentrated *in vacuo*. Purification of the residue by column chromatography afforded the cyclised product.

**Workup C**

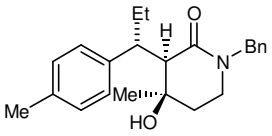
The reaction mixture was filtered through a short plug of $SiO_2$ (*ca*. 4 cm high x 2 cm diameter) using EtOAc as eluent (*ca.* 50 mL) and the filtrate was concentrated *in vacuo*. Purification of the residue by column chromatography afforded the cyclised product.




**(±)-(3*R*,4*R*)-1-Benzyl-4-hydroxy-4-methyl-3-[(*R*)-1-phenylpropyl]piperidin-2-one (174)**. The title compound was prepared according to General Procedure C from **173** (31 mg, 0.10 mmol) for a reaction time of 16 h followed by Workup C to give an off-white solid (33 mg, 98%) that required no further purification. Slow diffusion of hexane into a solution of **174** in EtOAc gave colourless crystals that were suitable for X-ray crystallography. $R_f$ = 0.34 (50% EtOAc/hexane); m.p. 155-156 °C; IR ($CHCl_3$) 3390 (OH), 2967, 1631 (C=O), 1495, 1453, 1381, 908, 733, 650, 622 $cm^{-1}$; $^1H$ NMR (360 MHz, $CDCl_3$) δ 7.45 (2H, dd, *J* = 8.1, 1.1 Hz, Ar**H**), 7.36-7.28 (7H, m, Ar**H**), 7.21 (1H, t, *J* = 7.3 Hz, Ar**H**), 4.67 (1H, d, *J* = 14.4 Hz, NC**H**$_2$Ar), 4.59 (1H, d, *J* = 14.4 Hz, NC**H**$_2$Ar), 3.34 (1H, ddd, *J* = 12.4, 6.8, 4.2 Hz, $CH_2$C**H**$_2$N), 3.09-3.01 (2H, m, $CH_2$C**H**$_2$N and C**H**$CH_2CH_3$), 2.86 (1H, app dd, *J* = 4.7, 1.7 Hz, C**H**C=O), 2.06-1.85 (2H, m, C**H**$_2$), 1.72-1.64 (3H, m, C**H**$_2$ and O**H**), 1.22 (3H, s, C**H**$_3$COH), 0.71 (3H, t, *J* = 7.6 Hz, C**H**$_3CH_2$); $^{13}C$ NMR (62.9 MHz, $CDCl_3$) δ 170.3 (C), 145.8 (C), 137.1 (C), 128.8 (2 x CH), 128.5 (4 x CH), 128.4 (2 x CH), 127.4 (CH), 126.3 (CH), 71.3 (C), 59.7 (CH), 50.2 ($CH_2$), 46.2 (CH), 43.4 ($CH_2$), 32.4 ($CH_2$), 28.4 ($CH_3$), 27.3 ($CH_2$), 12.6 ($CH_3$); HRMS (ES) Exact mass calcd for $C_{22}H_{28}NO_2$ $[M+H]^+$: 338.2115, found: 338.2116.

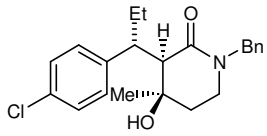



**(±)-(3*R*,4*R*)-1-Benzyl-4-hydroxy-3-[(*R*)-1-(4-methoxyphenyl)propyl]-4-methylpiperidin-2-one (193a)**. The title compound was prepared according to General Procedure C from **181** (67 mg, 0.20 mmol) for a reaction time of 3 h followed by Workup C to give a white solid (67 mg, 91%) that required no further purification. $R_f$ = 0.31 (50% EtOAc/hexane); m.p. 144-146 °C; IR ($CHCl_3$) 3019 (OH), 2962, 1631 (C=O), 1511, 1426, 1216, 1032, 929, 768, 669 $cm^{-1}$; $^1H$ NMR (360 MHz, $CDCl_3$) δ 7.36-7.27 (7H, m, Ar**H**), 6.85 (2H, d, *J* = 8.7 Hz, Ar**H**), 4.65 (1H, d, *J* = 14.4 Hz, NC**H**$_2$Ar), 4.57 (1H, d, *J* = 14.4 Hz, NC**H**$_2$Ar), 3.78 (3H, s, OC**H**$_3$), 3.32 (1H, ddd, *J* = 12.3, 6.7, 4.3 Hz, $CH_2$C**H**$_2$N), 3.07-2.99 (2H, m, $CH_2$C**H**$_2$N and C**H**$CH_2CH_3$), 2.80 (1H, app dd, *J* = 4.7, 1.6 Hz, C**H**C=O), 2.05-1.83 (3H, m, C**H**$_2$ and O**H**), 1.72-1.62 (2H, m, C**H**$_2$), 1.21 (3H, s, C**H**$_3$COH), 0.70 (3H, t, *J* = 7.3 Hz, C**H**$_3CH_2$); $^{13}C$ NMR (62.9 MHz, $CDCl_3$) δ 170.4 (C), 158.0 (C), 137.5 (C), 137.0 (C), 129.7 (2 x CH), 128.5 (2 x CH), 128.4 (2 x CH), 127.4 (CH), 113.9 (2 x CH), 71.3 (C), 59.7 (CH), 55.2 ($CH_3$), 50.1 ($CH_2$), 45.4 (CH), 43.3 ($CH_2$), 32.5 ($CH_2$), 28.4 ($CH_3$), 27.4 ($CH_2$), 12.5 ($CH_3$); HRMS (EI) Exact mass calcd for $C_{23}H_{29}NO_3$ $[M]^+$: 367.2142, found: 367.2138.

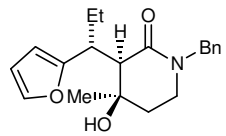



**(±)-(3*R*,4*R*)-1-Benzyl-4-hydroxy-4-methyl-3-[(*R*)-1-(4-methylphenyl)propyl]piperidin-2-one (193b)**. The title compound was prepared according to General Procedure C from **182** (32 mg, 0.10 mmol) for a reaction time of 18 h followed by Workup C and purification by column chromatography (40% EtOAc/hexane) to give a white solid (25 mg, 71%). $R_f$ = 0.37 (40% EtOAc/hexane); m.p. 148-150 °C; IR ($CHCl_3$) 3427 (OH), 1632 (C=O), 1453, 1381, 1265, 1095, 907, 849, 730, 650 $cm^{-1}$; $^1H$ NMR (360 MHz, $CDCl_3$) δ 7.36-7.28 (7H, m, Ar**H**), 7.13 (2H, d, *J* = 7.9 Hz, Ar**H**), 4.62 (1H, d, *J* = 14.4 Hz, NC**H**$_2$Ar), 4.54 (1H, d, *J* = 14.4 Hz, NC**H**$_2$Ar), 3.33 (1H, ddd, *J* = 12.4, 6.8, 4.1 Hz, $CH_2$C**H**$_2$N), 3.09-3.00 (2H, m, $CH_2$C**H**$_2$N and C**H**$CH_2CH_3$), 2.84 (1H, app dd, *J* = 5.1, 1.7 Hz, C**H**C=O), 2.33 (3H, s, C**H**$_3$Ar), 2.03 (1H, ddd, *J* = 13.4, 9.2, 6.8 Hz, C**H**$_2CH_2$N), 1.89 (1H, qdd, *J* = 14.5, 11.6, 7.3 Hz, CHC**H**$_2CH_3$), 1.71-1.63 (3H, m, C**H**$_2CH_2$N, CHC**H**$_2CH_3$ and O**H**), 1.21 (3H, s, C**H**$_3$COH), 0.70 (3H, t, *J* = 7.3 Hz, C**H**$_3CH_2$); $^{13}C$ NMR (62.9 MHz, $CDCl_3$) δ 170.4 (C), 142.4 (C), 137.1 (C), 135.9 (C), 129.3 (2 x CH), 128.6 (2 x CH), 128.6 (2 x CH), 128.4 (2 x CH), 127.4

(CH), 71.4 (C), 59.8 (CH), 50.2 ($CH_2$), 45.8 (CH), 43.4 ($CH_2$), 32.5 ($CH_2$), 28.4 ($CH_3$), 27.4 ($CH_2$), 21.0 ($CH_3$), 12.5 ($CH_3$); HRMS (EI) Exact mass calcd for $C_{23}H_{29}NO_2$ $[M]^+$: 351.2193, found: 351.2192.

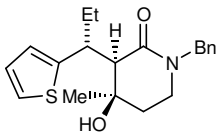



**(±)-(3*R*,4*R*)-1-Benzyl-3-[(*R*)-1-(4-chlorophenyl)propyl]4-hydroxy-4-methylpiperidin-2-one (193c)**. The title compound was prepared according to General Procedure C from **183** (34 mg, 0.10 mmol) for a reaction time of 18 h followed by Workup C and purification by column chromatography (40% EtOAc/hexane) to give a white solid (18 mg, 48%). $R_f$ = 0.35 (40% EtOAc/hexane); m.p. 165-168 °C; IR ($CHCl_3$) 3020 (OH), 1631 (C=O), 1522, 1476, 1424, 1218, 1015, 929, 771, 669 $cm^{-1}$; $^1H$ NMR (360 MHz, $CDCl_3$) δ 7.42 (2H, d, *J* = 8.4 Hz, Ar**H**), 7.34-7.26 (7H, m, Ar**H**), 4.68 (1H, d, *J* = 14.4 Hz, NC**H**$_2$Ar), 4.57 (1H, d, *J* = 14.4 Hz, NC**H**$_2$Ar), 3.35 (1H, ddd, *J* = 12.4, 6.4, 4.7 Hz, $CH_2$C**H**$_2$N), 3.10-3.02 (2H, m, $CH_2$C**H**$_2$N and C**H**$CH_2CH_3$), 2.77 (1H, app dd, *J* = 3.7, 1.6 Hz, C**H**C=O), 2.02-1.83 (2H, m, C**H**$_2$), 1.72-1.60 (3H, m C**H**$_2$ and O**H**), 1.25 (3H, s, C**H**$_3$COH), 0.71 (3H, t, *J* = 7.3 Hz, C**H**$_3$$CH_2$); $^{13}C$ NMR (62.9 MHz, $CDCl_3$) δ 169.9 (C), 144.8 (C), 137.0 (C), 130.3 (2 x CH), 128.6 (2 x CH), 128.5 (2 x CH), 128.4 (2 x CH), 127.5 (CH), 71.3 (C), 59.5 (CH), 50.2 ($CH_2$), 45.5 (CH), 43.3 ($CH_2$), 32.7 ($CH_2$), 28.7 ($CH_3$), 27.0 ($CH_2$), 12.6 ($CH_3$); HRMS (EI) Exact mass calcd for $C_{22}H_{26}NO_2Cl$ $[M]^+$: 371.1647, found: 371.1643.



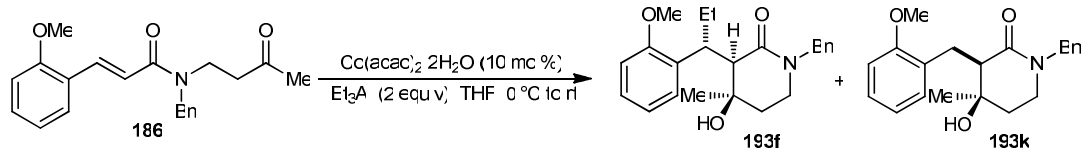

**(±)-(3*R*,4*R*)-1-Benzyl-3-[(*R*)-(1-furan-2-yl)propyl]-4-hydroxy-4-methylpiperidin-2-one (193d)**. The title compound was prepared according to General Procedure C from **184** (30 mg, 0.10 mmol) for a reaction time of 3 h followed by Workup C to give an off-white solid (25 mg, 76%) that required no further purification. $R_f$ = 0.31 (50% EtOAc/hexane); m.p. 168-170 °C; IR ($CHCl_3$) 3434 (OH), 1629 (C=O), 1454, 1381, 1262, 1096, 906, 736, 651, 506 $cm^{-1}$; $^1H$ NMR (360 MHz, $CDCl_3$) δ 7.34-7.25 (6H, m, Ar**H** and C**H**), 6.32 (1H, dd, *J* = 3.2, 1.9 Hz, C**H**), 6.17-6.16 (1H, m, C**H**), 4.67 (1H, d, *J* = 14.6 Hz, NC**H**$_2$Ar), 4.53 (1H, d, *J* = 14.6 Hz, NC**H**$_2$Ar), 3.64-3.58 (1H, m, C**H**$CH_2CH_3$), 3.29-3.23 (1H, m, $CH_2$C**H**$_2$N), 3.03 (1H, ddd, *J* = 12.4, 7.8, 5.9 Hz, $CH_2$C**H**$_2$N), 2.76 (1H, app d, *J* = 3.4 Hz, C**H**C=O), 2.15 (1H, ddq, *J* = 14.6, 10.9, 7.5

Hz, C**H**$_2$CH$_3$), 2.06 (1H, s, O**H**), 1.82 (1H, dqd, *J* = 14.6, 7.5, 4.6 Hz, C**H**$_2$CH$_3$), 1.69-1.62 (1H, m, C**H**$_2$CH$_2$N), 1.45 (1H, ddd, *J* = 13.6, 7.8, 6.1 Hz, C**H**$_2$CH$_2$N), 1.32 (3H, s, C**H**$_3$COH), 0.90 (3H, t, *J* = 7.5 Hz, C**H**$_3$CH$_2$); $^{13}$C NMR (62.9 MHz, $CDCl_3$) δ 170.3 (C), 156.6 (C), 140.9 (CH), 137.1 (C), 128.5 (2 x CH), 128.1 (2 x CH), 127.3 (CH), 110.7 (CH), 107.3 (CH), 70.9 (C), 57.1 (CH), 50.4 ($CH_2$), 43.2 ($CH_2$), 40.7 (CH), 34.2 ($CH_2$), 28.9 ($CH_3$), 26.5 ($CH_2$), 13.0 ($CH_3$); HRMS (ES) Exact mass calcd for $C_{20}H_{26}NO_3$ $[M+H]^+$: 328.1907, found: 327.1909.




**(±)-(3*R*,4*R*)-1-Benzyl-3-[(*R*)-(1-thiophen-2-yl)propyl]-4-hydroxy-4-methyl-3-[(*R*)-(1-thiophen-2-yl)propyl]piperidin-2-one (193e)**. The title compound was prepared according to General Procedure C from **185** (63 mg, 0.20 mmol) for a reaction time of 23 h followed by Workup B and purification by column chromatography (25% EtOAc/hexane→50% EtOAc/hexane) to give a white solid (58 mg, 85%). $R_f$ = 0.41 (40% EtOAc/hexane); m.p. 174-175 °C; IR ($CHCl_3$) 3402 (OH), 1797, 1649 (C=O), 1450, 1383, 1262, 1095, 908, 737, 650 cm$^{-1}$; $^1$H NMR (360 MHz, $CDCl_3$) δ 7.35-7.25 (5H, m, Ar**H**), 7.20 (1H, dd, *J* = 5.1, 1.2 Hz, C**H**), 6.99 (1H, dd, *J* = 3.5, 1.2, C**H**), 6.94 (1H, dd, *J* = 5.1, 3.5 Hz, C**H**), 4.68 (1H, d, *J* = 14.5 Hz, NC**H**$_2$Ar), 4.61 (1H, d, *J* = 14.5 Hz, NC**H**$_2$Ar), 3.63 (1H, ddd, *J* = 11.1, 3.7, 3.4 Hz, C**H**CH$_2$CH$_3$), 3.42-3.35 (1H, m, CH$_2$C**H**$_2$N), 3.05 (1H, ddd, *J* = 12.4, 6.3, 6.3 Hz, CH$_2$C**H**$_2$N), 2.80 (1H, app d, *J* = 3.4 Hz, C**H**C=O), 2.06 (1H, ddq, *J* = 14.4, 11.1, 7.3 Hz, CHC**H**$_2$CH$_3$), 1.88-1.69 (3H, m, CHC**H**$_2$CH$_3$ and C**H**$_2$CH$_2$N), 1.48 (1H, s, O**H**), 1.35 (3H, s, C**H**$_3$COH), 0.88 (3H, t, *J* = 7.3 Hz, C**H**$_3$CH$_2$); $^{13}$C NMR (62.9 MHz, $CDCl_3$) δ 169.7 (C), 149.0 (C), 137.0 (C), 128.5 (2 x CH), 128.2 (2 x CH), 127.3 (CH), 126.4 (CH), 125.0 (CH), 124.2 (CH), 71.4 (C), 58.8 (CH), 50.3 ($CH_2$), 43.0 ($CH_2$), 41.4 (CH), 34.4 ($CH_2$), 28.9 ($CH_3$), 28.4 ($CH_2$), 12.9 ($CH_3$); HRMS (EI) Exact mass calcd for $C_{20}H_{25}NO_2S$ $[M]^+$: 343.1601, found: 343.1600.

**(±)-(3*R*,4*R*)-1-Benzyl-4-hydroxy-3-[(*R*)-1-(2-methoxyphenyl)propyl]-4-methylpiperidin-2-one (193f) and (±)-(3*R*,4*R*)-1-benzyl-4-hydroxy-3-(2-methoxybenzyl)-4-methylpiperidin-2-one (193k)**

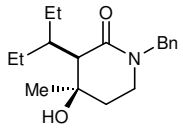



General Procedure C was followed using substrate **186** (67 mg, 0.20 mmol) for a reaction time of 30 h and the reaction mixture was subjected to Workup B followed by purification by column chromatography (20% EtOAc/hexane→50%EtOAc/hexane) to give the unreacted starting material **186** (11 mg, 16%), followed by the *alkylative aldol product* **193f** (15 mg, 21%) as a white solid, followed by the *reductive aldol product* **193k** (19 mg, 28%) as a white solid.

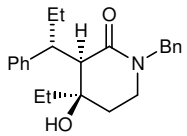
Data for **193f**: $R_f$ = 0.12 (30% EtOAc/hexane); m.p. 133-135 °C; IR ($CHCl_3$) 3389 (OH), 2924, 2854, 1625 (C=O), 1462, 1377, 1242, 1058, 846, 742 $cm^{-1}$; $^1H$ NMR (360 MHz, $CDCl_3$) δ 7.53 (1H, dd, *J* = 7.6, 1.4 Hz, Ar**H**), 7.35-7.28 (5H, m, Ar**H**), 7.20 (1H, ddd, *J* = 7.6, 4.8, 0.9 Hz, Ar**H**), 7.03 (1H, t, *J* = 7.6 Hz, Ar**H**), 6.88 (1H, d, *J* = 8.1 Hz, Ar**H**), 4.70 (1H, d, *J* = 14.3 Hz, NC**H**$_2$Ar), 4.53 (1H, d, *J* = 14.3 Hz, NC**H**$_2$Ar), 3.87 (3H, s, OC**H**$_3$), 3.46-3.41 (1H, m, C**H**CH$_2$CH$_3$), 3.31 (1H, ddd, *J* = 12.3, 7.0, 3.0 Hz, CH$_2$C**H**$_2$N), 3.05 (1H, ddd, *J* = 12.3, 10.1, 6.4 Hz, CH$_2$C**H**$_2$N), 2.79 (1H, app dd, *J* = 5.0, 1.5 Hz, C**H**C=O), 2.62 (1H, s, O**H**), 2.13 (1H, ddd, *J* = 13.2, 10.1, 7.0 Hz, C**H**$_2$CH$_2$N), 2.02-1.89 (1H, m, C**H**$_2$), 1.75-1.65 (2H, m, C**H**$_2$), 1.16 (3H, s, C**H**$_3$COH), 0.68 (3H, t, *J* = 7.3 Hz, C**H**$_3$CH$_2$); $^{13}C$ NMR (62.9 MHz, $CDCl_3$) δ 170.4 (C), 156.3 (C), 137.1 (C), 133.6 (C), 128. 8 (CH), 128.5 (4 x CH), 127.4 (CH), 127.1 (CH), 121.7 (CH), 110.5 (CH), 70.9 (C), 59.8 (CH), 55.5 ($CH_3$), 53.4 (CH), 50.0 ($CH_2$), 43.5 ($CH_2$), 32.3 ($CH_2$), 27.5 ($CH_3$), 26.0 ($CH_2$), 12.1 ($CH_3$); HRMS (ES) Exact mass calcd for $C_{23}H_{30}NO_3$ $[M+H]^+$: 368.2200, found: 368.2219.

Data for **193k**: $R_f$ = 0.06 (30% EtOAc/hexane); m.p. 145-147 °C; IR ($CHCl_3$) 3464 (OH), 3054, 2925, 1635 (C=O), 1495, 1453, 1265, 1111, 909, 737 $cm^{-1}$; $^1H$ NMR (360 MHz, $CDCl_3$) δ 7.38-7.19 (7H, m, Ar**H**), 6.93 (1H, dt, *J* = 7.5, 1.0 Hz, Ar**H**), 6.88 (1H, d, *J* = 8.2 Hz, Ar**H**), 4.72 (1H, d, *J* = 14.6 Hz, NC**H**$_2$Ar), 4.50 (1H, d, *J* = 14.6 Hz, NC**H**$_2$Ar), 3.90 (3H, s, OC**H**$_3$), 3.38-3.29 (3H, m, CH$_2$C**H**$_2$N and CHC**H**$_2$ and O**H**), 3.19 (1H, dd, *J* = 14.3, 7.6 Hz, CHC**H**$_2$), 3.03 (1H, ddd, *J* = 12.1, 5.9, 5.9

Hz, $CH_2CH_2N$), 2.75 (1H, app dd, *J* = 7.6, 4.8 Hz, C**H**C=O), 1.76-1.66 (2H, m, $CH_2CH_2N$), 1.07 (3H, s, $CH_3COH$); $^{13}C$ NMR (62.9 MHz, $CDCl_3$) δ 171.1 (C), 156.3 (C), 137.2 (C), 131.6 (CH), 129.4 (C), 128.5 (2 x CH), 128.0 (2 x CH), 127.6 (CH), 127.2 (CH), 121.5 (CH), 110.7 (CH), 69.9 (C), 55.5 ($CH_3$), 54.0 (CH), 50.4 ($CH_2$), 43.0 ($CH_2$), 34.9 ($CH_2$), 28.5 ($CH_3$), 27.4 ($CH_2$); HRMS (ES) Exact mass calcd for $C_{21}H_{26}NO_3$ $[M+H]^+$: 340.1907, found: 340.1909.

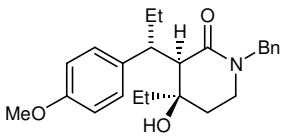



**(±)-(3*R*,4*R*)-1-Benzyl-4-hydroxy-3-(1-ethylpropyl)-4-methylpiperidin-2-one (193g)**. General Procedure C was followed using substrate from **187** (70 mg, 0.20 mmol) for a reaction time of 16 h followed by Workup B and purification by column chromatography (30% EtOAc/hexane) to give unreacted starting material **187** (17 mg, 35%) followed by the *alkylative aldol product* **193g** (20 mg, 35%) as a white solid. $R_f$ = 0.18 (30% EtOAc/hexane); m.p. 132-135 °C; IR ($CHCl_3$) 3419 (OH), 2959, 2872, 1622 (C=O), 1455, 1426, 1378, 1264, 911, 651 $cm^{-1}$; $^1H$ NMR (360 MHz, $CDCl_3$) δ 7.34-7.24 (5H, m, Ar**H**), 4.65 (1H, d, *J* = 14.5 Hz, NC**H**$_2$Ar), 4.53 (1H, d, *J* = 14.5 Hz, NC**H**$_2$Ar), 3.47 (1H, ddd, *J* = 12.3, 9.0, 4.9 Hz, $CH_2CH_2N$), 3.04 (1H, ddd, *J* = 12.3, 5.5, 5.5 Hz, $CH_2CH_2N$), 2.42 (1H, app s, C**H**C=O), 1.89-1.42 (7H, m, $CH_2CH_2N$ and C**H**(C**H**$_2$CH$_3$)$_2$), 1.39 (1H, s, O**H**), 1.29 (3H, s, $CH_3COH$), 0.98 (3H, t, *J* = 6.2 Hz, $CH_3CH_2$), 0.94 (3H, t, *J* = 6.2 Hz, $CH_3CH_2$); $^{13}C$ NMR (62.9 MHz, $CDCl_3$) δ 170.5 (C), 137.3 (C), 128. 5 (2 x CH), 128.2 (2 x CH), 127.3 (CH), 71.2 (C), 52.9 (CH), 50.0 ($CH_2$), 42.8 ($CH_2$), 41.4 (CH), 35.3 ($CH_2$), 29.2 ($CH_3$), 26.6 ($CH_2$), 25.3 ($CH_2$), 13.2 ($CH_3$), 12.3 ($CH_3$); HRMS (ES) Exact mass calcd for $C_{18}H_{28}NO_2$ $[M+H]^+$: 290.2115, found 290.2114.



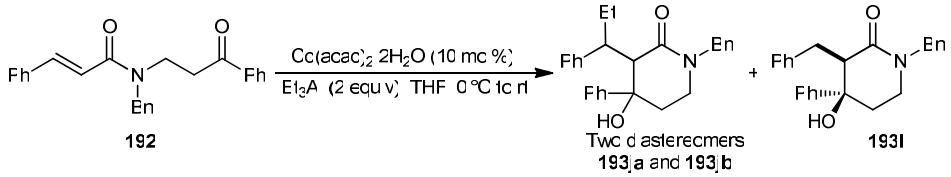

**(±)-(3*R*,4*R*)-1-Benzyl-4-ethyl-4-hydroxy-3-[(*R*)-1-phenylpropyl]piperidin-2-one (193h)**. The title compound was prepared according to General Procedure C from **188** (64 mg, 0.20 mmol) for a reaction time of 16 h followed by Workup B and purification by column chromatography (25% EtOAc and 0.5% $Et_3N$ in hexane) to give a white solid (42 mg, 60%). Slow diffusion of petrol into a solution of **193h** in $CH_2Cl_2$ gave colourless crystals that were suitable for X-ray crystallography. $R_f$ = 0.45 (40% EtOAc/hexane);

m.p. 188-189 °C; IR ($CHCl_3$) 3580 (OH), 2967, 1631 (C=O), 1494, 1452, 1380, 1096, 908, 732, 649 $cm^{-1}$; $^1H$ NMR (360 MHz, $CDCl_3$) δ 7.43 (2H, d, *J* = 7.9 Hz, Ar**H**), 7.38-7.29 (7H, m, Ar**H**), 7.20 (1H, t, *J* = 7.3 Hz, Ar**H**), 4.68 (1H, d, *J* = 14.4 Hz, NC**H**$_2$Ar), 4.56 (1H, d, *J* = 14.4 Hz, NC**H**$_2$Ar), 3.29 (1H, ddd, *J* = 12.4, 6.7, 3.7 Hz, $CH_2$C**H**$_2$N), 3.07-2.96 (2H, m, $CH_2$C**H**$_2$N and C**H**$CH_2CH_3$), 2.90 (1H, app dd, *J* = 5.1, 1.8 Hz, C**H**C=O), 2.01-1.82 (2H, m, C**H**$_2$), 1.77-1.62 (2H, m, C**H**$_2$), 1.55-1.36 (2H, m, $CH_3$C**H**$_2$COH), 1.16 (1H, s, O**H**), 0.83 (3H, t, *J* = 7.4 Hz, C**H**$_3CH_2$COH), 0.69 (3H, t, *J* = 7.3 Hz, C**H**$_3CH_2$CH); $^{13}C$ NMR (62.9 MHz, $CDCl_3$) δ 170.4 (C), 146.0 (C), 137.1 (C), 128.7 (2 x CH), 128.6 (2 x CH), 128.5 (2 x CH), 128.4 (2 x CH), 127.4 (CH), 126.2 (CH), 73.2 (C), 58.7 (CH), 50.1 ($CH_2$), 46.2 (CH), 43.2 ($CH_2$), 32.5 ($CH_2$), 28.9 ($CH_2$), 27.4 ($CH_2$), 12.5 ($CH_3$), 7.0 ($CH_3$); HRMS (EI) Exact mass calcd for $C_{23}H_{29}NO_2$ $[M]^+$: 351.2193, found: 351.2196.




**(±)-(3*R*,4*R*)-1-Benzyl-4-ethyl-4-hydroxy-3-[(*R*)-1-(4-methoxyphenyl)propyl]piperidin-2-one (193i)**. The title compound was prepared according to General Procedure C from **189** (70 mg, 0.20 mmol) for a reaction time of 16 h followed by Workup B and purification by column chromatography (30% EtOAc and 0.5% $Et_3N$ in hexane) to give a white solid (53 mg, 70%). $R_f$ = 0.41 (40% EtOAc/hexane); m.p. 178-179 °C; IR ($CHCl_3$) 3583 (OH), 2966, 1632 (C=O), 1511, 1453, 1251, 1179, 902, 740, 651 $cm^{-1}$; $^1H$ NMR (360 MHz, $CDCl_3$) δ 7.36-7.28 (7H, m, Ar**H**), 6.85 (2H, d, *J* = 8.8 Hz, Ar**H**), 4.68 (1H, d, *J* = 14.4 Hz, NC**H**$_2$Ar), 4.54 (1H, d, *J* = 14.4 Hz, NC**H**$_2$Ar), 3.79 (3H, s, OC**H**$_3$), 3.28 (1H, ddd, *J* = 12.4, 6.7, 3.7 Hz, $CH_2$C**H**$_2$N), 3.03-2.97 (2H, m, $CH_2$C**H**$_2$N and C**H**$CH_2CH_3$), 2.86 (1H, app dd, *J* = 5.3, 1.7 Hz, C**H**C=O), 2.00-1.80 (2H, m, C**H**$_2$), 1.76-1.63 (2H, m, C**H**$_2$), 1.52-1.37 (2H, m, $CH_3$C**H**$_2$COH), 1.24 (1H, s, O**H**), 0.84 (3H, t, *J* = 7.4 Hz, C**H**$_3CH_2$COH), 0.69 (3H, t, *J* = 7.3 Hz, C**H**$_3CH_2$CH); $^{13}C$ NMR (62.9 MHz, $CDCl_3$) δ 170.6 (C), 158.0 (C), 137.6 (C), 137.1 (C), 129.6 (2 x CH), 128.6 (2 x CH), 128.4 (2 x CH), 127.4 (CH), 114.0 (2 x CH), 73.2 (C), 58.7 (CH), 55.2 ($CH_3$), 50.1 ($CH_2$), 45.5 (CH), 43.2 ($CH_2$), 32.6 ($CH_2$), 29.1 ($CH_2$), 27.6 ($CH_2$), 12.5 ($CH_3$), 7.0 ($CH_3$)**;** HRMS (ES) Exact mass calcd for $C_{24}H_{32}NO_3$ $[M+H]^+$: 382.2377, found: 382.2376.

**1-Benzyl-4-hydroxy-4-phenyl-3-(1-phenylpropyl)piperidin-2-one (two diastereomers 193ja and 193jb) and (±)-(3*R*,4*R*)-1,3-dibenzyl-4-hydroxy-4-phenylpiperidin-2-one (193l)**



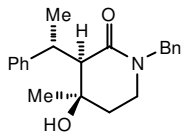

General Procedure C was followed using substrate **192** (74 mg, 0.20 mmol) for a reaction time of 48 h and the reaction mixture was subjected to Workup B followed by purification by column chromatography (10% EtOAc/hexane) to give one diastereomer of the *alkylative aldol product* **193ja** (21 mg, 27%) as a white solid, followed by a second diastereomer of the *alkylative aldol product* **193jb** (20 mg, 25%) as a white solid, followed by the *reductive aldol product* **193l** (19 mg, 26%) as a white solid.

Data for **193ja**: $R_f$ = 0.37 (20% EtOAc/hexane); m.p. 146-148 °C; IR ($CHCl_3$) 3367 (OH), 1793, 1631 (C=O), 1489, 1452, 1377, 1093, 906, 737, 650 $cm^{-1}$; $^1H$ NMR (360 MHz, $CDCl_3$) δ 7.43-7.39 (5H, m, Ar**H**), 7.35-7.19 (10H, m, Ar**H**), 4.77 (1H, d, *J* = 14.8 Hz, NC**H**$_2$Ar), 4.53 (1H, d, *J* = 14.8 Hz, NC**H**$_2$Ar), 3.41-3.33 (2H, m, $CH_2$C**H**$_2$N and C**H**C=O), 2.94 (1H, ddd, *J* = 12.0, 5.8, 3.7 Hz, $CH_2$C**H**$_2$N), 2.81 (1H, ddd, *J* = 9.1, 6.5, 2.8 Hz, C**H**C$H_2$C$H_3$), 2.34-2.14 (2H, m, C**H**$_2$), 2.10-2.02 (2H, m, C**H**$_2$ and O**H**), 1.83 (1H, ddd, *J* = 13.9, 5.1, 3.7 Hz, C**H**$_2$C$H_2$N), 0.72 (3H, t, *J* = 7.4 Hz, C**H**$_3$C$H_2$); $^{13}C$ NMR (62.9 MHz, $CDCl_3$) δ 170.0 (C), 146.2 (C), 143.3 (C), 137.0 (C), 130.1 (2 x CH), 128.8 (2 x CH), 128.6 (2 x CH), 128.5 (2 x CH), 127.8 (2 x CH), 127.2 (CH), 127.1 (CH), 127.1 (CH), 124.7 (2 x CH), 76.3 (C), 54.9 (CH), 50.5 ($CH_2$), 47.0 (CH), 43.7 ($CH_2$), 36.8 ($CH_2$), 30.8 ($CH_2$), 13.0 ($CH_3$); HRMS (EI) Exact mass calcd for $C_{27}H_{29}NO_2$ $[M]^+$: 399.2193, found: 399.2193.

Data for **193jb**: $R_f$ = 0.34 (20% EtOAc/hexane); m.p. 169-171 °C; IR ($CHCl_3$) 3394 (OH), 1631 (C=O), 1497, 1452, 1383, 1099, 1028, 908, 733, 650 $cm^{-1}$; $^1H$ NMR (360 MHz, $CDCl_3$) δ 7.42-7.15 (15H, m, Ar**H**), 4.71 (1H, d, *J* = 14.6 Hz, NC**H**$_2$Ar), 4.62 (1H, d, *J* = 14.6 Hz, NC**H**$_2$Ar), 3.46 (1H, ddd, *J* = 12.2, 8.5, 5.2 Hz, $CH_2$C**H**$_2$N), 3.33-3.26 (2H, m, C**H**C=O and C**H**C$H_2$C$H_3$), 2.93-2.87 (1H, m, $CH_2$C**H**$_2$N), 2.18 (1H, ddd, *J* = 14.4, 7.3, 3.5 Hz, C**H**$_2$C$H_3$), 2.05-1.90 (2H, m, C**H**$_2$), 1.83 (1H, s, O**H**), 1.66-1.60 (1H, m, C**H**$_2$), 0.72 (3H, t, *J* = 7.3 Hz, C**H**$_3$C$H_2$); $^{13}C$ NMR (62.9 MHz,

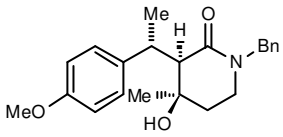
$CDCl_3$) δ 170.0 (C), 145.5 (C), 145.2 (C), 137.0 (C), 129.0 (2 x CH), 128.5 (2 x CH), 128.4 (2 x CH), 128.3 (2 x CH), 128.1 (2 x CH), 127.5 (CH), 127.3 (CH), 126.2 (CH), 125.1 (2 x CH), 75.7 (C), 57.4 (CH), 50.5 ($CH_2$), 45.5 (CH), 43.4 ($CH_2$), 35.6 ($CH_2$), 26.5 ($CH_2$), 13.0 ($CH_3$); HRMS (ES) Exact mass calcd for $C_{27}H_{30}NO_2$ $[M+H]^+$: 400.2271, found: 400.2267.

Data for **193l**: $R_f$ = 0.17 (20% EtOAc/hexane); m.p. 180-182 °C; IR ($CHCl_3$) 3397 (OH), 1635 (C=O), 1494, 1453, 1382, 1265, 1095, 908, 734, 651 $cm^{-1}$; $^1H$ NMR (360 MHz, $CDCl_3$) δ 7.43-7.26 (10H, m, Ar**H**), 7.21-7.10 (3H, m, Ar**H**), 7.07-7.05 (2H, m, Ar**H**), 4.74 (1H, d, *J* = 14.8 Hz, NC**H**$_2$Ar), 4.68 (1H, d, *J* = 14.8 Hz, NC**H**$_2$Ar), 3.56 (1H, ddd, *J* = 11.5, 11.1, 5.1 Hz, $CH_2$C**H**$_2$N), 3.23 (1H, dd, *J* = 6.0, 3.7 Hz, C**H**$CH_2$Ph), 3.18-3.11 (1H, m, $CH_2$C**H**$_2$N), 3.09-3.01 (2H, m, CHC**H**$_2$Ph), 2.25 (1H, ddd, *J* = 14.0, 11.1, 6.1 Hz, C**H**$_2CH_2$N), 2.02 (1H, s, O**H**), 1.94 (1H, ddd, *J* = 14.0, 5.1, 2.9 Hz, C**H**$_2CH_2$N); $^{13}C$ NMR (62.9 MHz, $CDCl_3$) δ 171.0 (C), 145.5 (C), 141.1 (C), 137.1 (C), 129.5 (2 x CH), 128.5 (4 x CH), 128.3 (2 x CH), 127.8 (2 x CH), 127.3 (2 x CH), 126.0 (CH), 124.7 (2 x CH), 75.9 (C), 53.4 (CH), 50.5 ($CH_2$), 43.5 ($CH_2$), 37.0 ($CH_2$), 31.9 ($CH_2$); HRMS (EI) Exact mass calcd for $C_{25}H_{22}NO_2$ $[M]^+$: 371.1880, found: 371.1880.

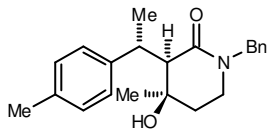



**(±)-(3*R*,4*R*)-1-Benzyl-4-hydroxy-4-methyl-3-[(*R*)-1-phenylethyl]piperidin-2-one (194a)**. The title compound was prepared according to General Procedure D from **173** (31 mg, 0.10 mmol) for a reaction time of 24 h followed by Workup C and purification by column chromatography (90% $Et_2O$/hexane) to give a white solid (14 mg, 43%). $R_f$ = 0.28 (90% $Et_2O$/hexane); m.p. 166-167 °C; IR ($CHCl_3$) 3155 (OH), 1793, 1632 (C=O), 1494, 1382, 1095, 902, 722, 651, 623 $cm^{-1}$; $^1H$ NMR (360 MHz, $CDCl_3$) δ 7.47 (2H, d, *J* = 8.3 Hz, Ar**H**), 7.35-7.30 (7H, m, Ar**H**), 7.20 (1H, t, *J* = 7.2 Hz, Ar**H**), 4.67 (1H, d, *J* = 14.4 Hz, NC**H**$_2$Ar), 4.60 (1H, d, *J* = 14.4 Hz, NC**H**$_2$Ar), 3.47-3.31 (2H, m, C**H**$CH_3$ and $CH_2$C**H**$_2$N), 3.06 (1H, ddd, *J* = 12.5, 9.0, 6.3 Hz, $CH_2$C**H**$_2$N), 2.85 (1H, dd, *J* = 4.6, 1.7 Hz, C**H**C=O), 2.04 (1H, ddd, *J* = 13.4, 9.0, 6.7 Hz, C**H**$_2CH_2$N), 1.71 (1H, dddd, *J* = 13.4, 6.3, 4.6, 1.7 Hz, C**H**$_2CH_2$N), 1.38 (3H, d, *J* = 7.6 Hz, C**H**$_3$CH), 1.29 (1H, s, O**H**), 1.27 (3H, s, C**H**$_3$COH); $^{13}C$ NMR (62.9 MHz, $CDCl_3$) δ 170.1 (C), 148.1 (C), 137.1 (C), 128.7 (2 x CH), 128.6 (2 x CH), 128.4 (2 x CH),

127.8 (2 x CH), 127.5 (CH), 126.2 (CH), 71.4 (C), 59.3 (CH), 50.1 ($CH_2$), 43.3 ($CH_2$), 38.2 (CH), 32.7 ($CH_2$), 28.6 ($CH_3$), 21.0 ($CH_3$); HRMS (ES) Exact mass calcd for $C_{21}H_{26}NO_2$ $[M+H]^+$: 324.1958, found: 324.1956.

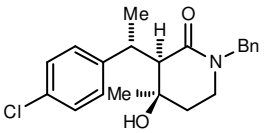



**(±)-(3*R*,4*R*)-1-Benzyl-4-hydroxy-3-[(*R*)-1-(4-methoxyphenyl)ethyl]-4-methylpiperidin-2-one (194b)**. The title compound was prepared according to General Procedure D from **181** (67 mg, 0.20 mmol) for a reaction time of 22 h followed by Workup A and purification by column chromatography (50% EtOAc/hexane) to give a white solid (34 mg, 48%). $R_f$ = 0.28 (50% EtOAc/hexane); m.p. 165-166 °C; IR ($CHCl_3$) 3389 (OH), 1624 (C=O), 1511, 1453, 1246, 1179, 1036, 908, 732, 649 $cm^{-1}$; $^1$H NMR (360 MHz, $CDCl_3$) δ 7.36-7.23 (7H, m, Ar**H**), 6.83 (2H, d, *J* = 8.8 Hz, Ar**H**), 4.63 (1H, d, *J* = 14.4 Hz, NC**H**$_2$Ar), 4.56 (1H, d, *J* = 14.4 Hz, NC**H**$_2$Ar), 3.76 (3H, s, OC**H**$_3$), 3.38-3.29 (2H, m, $CH_2$C**H**$_2$N and C**H**$CH_3$), 3.02 (1H, ddd, *J* = 12.5, 8.8, 6.3 Hz, $CH_2$C**H**$_2$N), 2.76 (1H, app dd, *J* = 4.6, 1.5 Hz, C**H**C=O), 1.99 (1H, ddd, *J* = 13.6, 8.8, 6.7 Hz, C**H**$_2$$CH_2$N), 1.69-1.63 (1H, m, C**H**$_2$$CH_2$N), 1.41 (1H, s, O**H**), 1.33 (3H, d, *J* = 7.3 Hz, C**H**$_3$CH), 1.24 (3H, s, C**H**$_3$COH); $^{13}$C NMR (62.9 MHz, $CDCl_3$) δ 170.3 (C), 158.0 (C), 139.9 (C), 137.1 (C), 128.8 (2 x CH), 128.6 (2 x CH), 128.4 (2 x CH), 127.4 (CH), 114.0 (2 x CH), 71.4 (C), 59.4 (CH), 55.2 ($CH_3$), 50.1 ($CH_2$), 43.3 ($CH_2$), 37.4 (CH), 32.9 ($CH_2$), 28.5 ($CH_3$), 21.2 ($CH_3$); HRMS (EI) Exact mass calcd for $C_{22}H_{27}NO_3$ $[M]^+$: 353.1985, found: 353.1988.

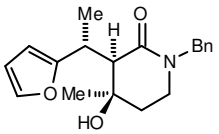



**(±)-(3*R*,4*R*)-1-Benzyl-4-hydroxy-4-methyl-3-(1-*p*-tolylethyl)piperidin-2-one (194c)**. The title compound was prepared according to General Procedure D from **182** (64 mg, 0.20 mmol) for a reaction time of 16 h followed by Workup A and purification by column chromatography (30% EtOAc/hexane) to give a white solid (31 mg, 46%). $R_f$ = 0.34 (50% EtOAc/hexane); m.p. 161-163 °C; IR ($CHCl_3$) 3583 (OH), 2972, 1632 (C=O), 1453, 1381, 1265, 1094, 907, 731, 650 $cm^{-1}$; $^1$H NMR (360 MHz, $CDCl_3$) δ 7.36-7.28 (7H, m, Ar**H**), 7.14 (2H, d, *J* = 7.8 Hz, Ar**H**), 4.66 (1H, d, *J* = 14.4 Hz, NC**H**$_2$Ar), 4.59 (1H, d, *J* = 14.4 Hz, NC**H**$_2$Ar), 3.41-3.32 (2H, m, $CH_2$C**H**$_2$N and C**H**$CH_3$), 3.05 (1H, ddd, *J* = 12.5, 9.0, 6.3 Hz, $CH_2$C**H**$_2$N), 2.83 (1H, dd, *J* = 5.0, 1.6

Hz, C**H**C=O), 2.33 (3H, s, C**H**$_3$Ar), 2.04 (1H, ddd, *J* = 13.5, 9.0, 6.7 Hz, C**H**$_2$CH$_2$N), 1.73-1.66 (1H, m, C**H**$_2$CH$_2$N), 1.36 (3H, d, *J* = 7.3 Hz, C**H**$_3$CH), 1.35 (1H, s, O**H**), 1.25 (3H, s, C**H**$_3$COH); $^{13}$C NMR (62.9 MHz, $CDCl_3$) δ 170.3 (C), 144.9 (C), 137.1 (C), 135.8 (C), 129.4 (2 x CH), 128.6 (2 x CH), 128.4 (2 x CH), 127.6 (2 x CH), 127.4 (CH), 71.4 (C), 59.4 (CH), 50.1 ($CH_2$), 43.3 ($CH_2$), 37.9 (CH), 32.7 ($CH_2$), 28.5 ($CH_3$), 21.2 ($CH_3$), 20.9 ($CH_3$); HRMS (EI) Exact mass calcd for $C_{22}H_{27}NO_2$ $[M]^+$: 337.2036, found: 337.2034.

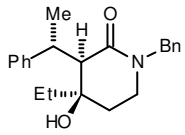



**(±)-(3*R*,4*R*)-1-Benzyl-3-[1-(4-chlorophenyl)ethyl]-4-hydroxy-4-methylpiperidin-2-one (194d)**. The title compound was prepared according to General Procedure D from **183** (103 mg, 0.30 mmol) for a reaction time of 24 h followed by Workup C and purification by column chromatography (40% EtOAc/hexane) to give a white solid (19 mg, 18%). $R_f$ = 0.32 (40% EtOAc/hexane); m.p. 169-171 °C; IR ($CHCl_3$) 3155 (OH), 2980, 1793, 1634 (C=O), 1468, 1381, 1091, 903, 737, 650 cm$^{-1}$; $^1$H NMR (360 MHz, $CDCl_3$) δ 7.42 (2H, d, *J* = 8.4 Hz, Ar**H**), 7.36-7.26 (7H, m, Ar**H**), 4.65 (1H, d, *J* = 14.5 Hz, NC**H**$_2$Ar), 4.60 (1H, d, *J* = 14.5 Hz, NC**H**$_2$Ar), 3.44-3.34 (2H, m, CH$_2$C**H**$_2$N and C**H**CH$_3$), 3.06 (1H, ddd, *J* = 12.5, 8.5, 6.1 Hz, CH$_2$C**H**$_2$N), 2.76 (1H, dd, *J* = 3.6, 1.5 Hz, C**H**C=O), 2.06 (1H, s, O**H**), 2.05-1.96 (1H, m, C**H**$_2$CH$_2$N), 1.75-1.67 (1H, m, C**H**$_2$CH$_2$N), 1.36 (3H, d, *J* = 7.3 Hz, C**H**$_3$CH), 1.29 (3H, s, C**H**$_3$COH); $^{13}$C NMR (62.9 MHz, $CDCl_3$) δ 169.8 (C), 147.0 (C), 137.0 (C), 131.7 (C), 129.3 (2 x CH), 128.6 (2 x CH), 128.5 (2 x CH), 128.3 (2 x CH), 127.5 (CH), 71.3 (C), 58.9 (CH), 50.1 ($CH_2$), 43.2 ($CH_2$), 37.4 (CH), 33.0 ($CH_2$), 28.8 ($CH_3$), 20.3 ($CH_3$)**;** HRMS (EI) Exact mass calcd for $C_{21}H_{24}NO_2Cl$ $[M]^+$: 357.1490, found: 357.1492.



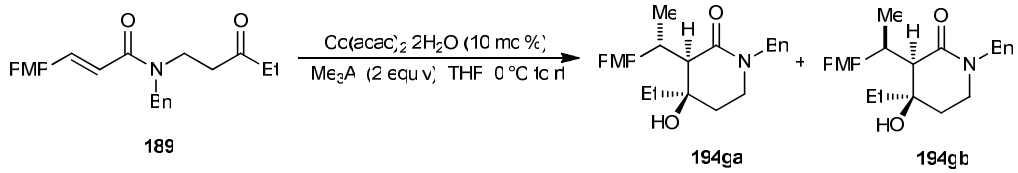

**(±)-(3*R*,4*R*)-1-Benzyl-3-(1-furan-2-ylethyl)-4-hydroxy-4-methylpiperidin-2-one (194e)**. The title compound was prepared according to General Procedure D from **184** (59 mg, 0.20 mmol) for a reaction time of 18 h followed by Workup C and purification by column chromatography (50% EtOAc/hexane) to give a white solid (25 mg, 40%). $R_f$ = 0.24 (50% EtOAc/hexane); m.p. 168-170 °C; IR ($CHCl_3$) 3062 (OH), 1693 (C=O), 1601,

1494, 1368, 1266, 1226, 909, 736, 702 $cm^{-1}$; $^1H$ NMR (360 MHz, $CDCl_3$) δ 7.32-7.27 (6H, m, Ar**H** and C**H**), 6.32 (1H, dd, *J* = 3.2, 1.9 Hz, C**H**), 6.15 (1H, dt, *J* = 3.2, 0.9 Hz, C**H**), 4.69 (1H, d, *J* = 14.6 Hz, NC**H**$_2$Ar), 4.53 (1H, d, *J* = 14.6 Hz, NC**H**$_2$Ar), 3.75 (1H, dq, *J* = 7.4, 2.6 Hz, C**H**$CH_3$), 3.35 (1H, ddd, *J* = 12.6, 6.8, 5.9 Hz, $CH_2$C**H**$_2$N), 3.05 (1H, ddd, *J* = 12.6, 6.9, 6.0 Hz, $CH_2$C**H**$_2$N), 2.83 (1H, app d, *J* = 2.6 Hz, C**H**C=O), 1.75-1.61 (3H, m, C**H**$_2CH_2$N and O**H**), 1.50 (3H, d, *J* = 7.4 Hz, C**H**$_3$CH), 1.36 (3H, s, C**H**$_3$COH); $^{13}C$ NMR (62.9 MHz, $CDCl_3$) δ 169.6 (C), 159.1 (C), 140.6 (CH), 137.1 (CH), 128.5 (2 x CH), 128.2 (2 x CH), 127.3 (CH), 110.6 (CH), 105.1 (CH), 71.1 (C), 56.4 (CH), 50.2 ($CH_2$), 43.0 ($CH_2$), 34.5 ($CH_2$), 32.0 (CH), 29.1 ($CH_3$), 17.7 ($CH_3$)**;** HRMS (ESI) Exact mass calcd for $C_{19}H_{24}NO_3$ $[M+H]^+$: 314.1751, found: 314.1747.




**(±)-(3*R*,4*R*)-1-Benzyl-4-ethyl-4-hydroxy-3-(1-phenylethyl)piperidin-2-one (194f)**. The title compound was prepared according to General Procedure D from **188** (96 mg, 0.30 mmol) for a reaction time of 48 h followed by Workup C and purification by column chromatography (30% EtOAc/hexane, then a second column using 20% acetone/petrol) to give a white solid (26 mg, 26%). $R_f$ = 0.39 (40% EtOAc/hexane); m.p. 161-164 °C; IR ($CHCl_3$) 3583 (OH), 2970, 2253, 1631 (C=O), 1494, 1452, 1094, 905, 728, 651 $cm^{-1}$; $^1H$ NMR (360 MHz, $CDCl_3$) δ 7.45 (2H, d, *J* = 7.9 Hz, Ar**H**), 7.35-7.29 (7H, m, Ar**H**), 7.20 (1H, t, *J* = 7.3 Hz, Ar**H**), 4.75 (1H, d, *J* = 14.4 Hz, NC**H**$_2$Ar), 4.50 (1H, d, *J* = 14.4 Hz, NC**H**$_2$Ar), 3.41-3.28 (2H, m, $CH_2$C**H**$_2$N), 3.05-2.97 (1H, m, C**H**$CH_3$), 2.89 (1H, dd, *J* = 5.0, 1.7 Hz, C**H**C=O), 2.03-1.95 (1H, m, C**H**$_2CH_2$N), 1.79-1.67 (1H, m, C**H**$_2CH_2$N), 1.57-1.43 (2H, m, $CH_3$C**H**$_2$COH), 1.36 (3H, d, *J* = 7.3 Hz, C**H**$_3$CH), 1.19 (1H, s, O**H**), 0.86 (3H, t, *J* = 7.4 Hz, C**H**$_3CH_2$COH); $^{13}C$ NMR (62.9 MHz, $CDCl_3$) δ 170.3 (C), 148.3 (C), 137.1 (C), 128.6 (3 x CH), 128.4 (2 x CH), 127.7 (2 x CH), 127.4 (2 x CH), 126.1 (CH), 73.1 (C), 58.1 (CH), 50.1 ($CH_2$), 43.1 ($CH_2$), 38.3 (CH), 32.6 ($CH_2$), 29.2 ($CH_2$), 21.2 ($CH_3$), 7.1 ($CH_3$); HRMS (EI) Exact mass calcd for $C_{22}H_{27}NO_2$ $[M]^+$: 337.2036, found: 337.2038.

**1-Benzyl-4-ethyl-4-hydroxy-3-[1-(4-methoxy-phenyl)-ethyl]-piperidin-2-one (194ga and 194gb).**



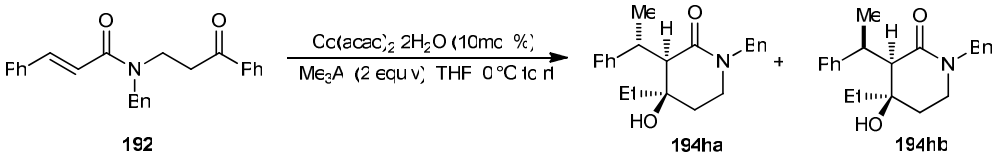

General Procedure D was followed using substrate **189** (105 mg, 0.30 mmol) for a reaction time of 46 h and the reaction mixture was subjected to Workup B followed by purification by column chromatography (40% EtOAc/hexane) to give the major diastereomeric product **194ga** (26 mg, 34%) as a white solid, followed by the minor diastereomeric product **194gb** (19 mg, 17%) as a white solid.

Data for **194ga**: $R_f$ = 0.35 (40% EtOAc/hexane); m.p. 136-138 °C; IR ($CHCl_3$) 3583 (OH), 2967, 2252, 1630 (C=O), 1512, 1453, 1248, 907, 732, 650 $cm^{-1}$; $^1H$ NMR (360 MHz, $CDCl_3$) δ 7.37-7.28 (7H, m, Ar**H**), 6.86 (2H, t, *J* = 8.8 Hz, Ar**H**), 4.74 (1H, d, *J* = 14.4 Hz, NC**H**$_2$Ar), 4.48 (1H, d, *J* = 14.4 Hz, NC**H**$_2$Ar), 3.79 (3H, s, OC**H**$_3$), 3.37-3.27 (2H, m, $CH_2$C**H**$_2$N and C**H**$CH_3$), 3.04-2.96 (1H, m, $CH_2$C**H**$_2$N), 2.84 (1H, dd, *J* = 5.1, 1.6 Hz, C**H**C=O), 2.01-1.93 (1H, m, C**H**$_2CH_2$N), 1.77-1.70 (1H, m, C**H**$_2CH_2$N), 1.56-1.43 (2H, m, $CH_3$C**H**$_2$COH), 1.34 (3H, d, *J* = 7.3 Hz, C**H**$_3$CH), 1.31 (1H, s, O**H**), 0.86 (3H, t, *J* = 7.4 Hz, C**H**$_3CH_2$COH); $^{13}C$ NMR (62.9 MHz, $CDCl_3$) δ 170.5 (C), 157.9 (C), 140.2 (C), 137.1 (C), 128.7 (2 x CH), 128.6 (2 x CH), 128.4 (2 x CH), 127.4 (CH), 114.1 (2 x CH), 73.2 (C), 58.2 (CH), 55.2 ($CH_3$), 50.1 ($CH_2$), 43.1 (CH), 37.5 ($CH_3$), 32.6 ($CH_2$), 29.3 ($CH_2$), 21.5 ($CH_2$), 7.1 ($CH_3$); HRMS (ES) Exact mass calcd for $C_{23}H_{30}NO_3$ $[M+H]^+$: 368.2220, found: 368.2223.

Data for **194gb**: $R_f$ = 0.21 (40% EtOAc/hexane); m.p. 118-120 °C; IR ($CHCl_3$) 3399 (OH), 2929, 1620 (C=O), 1512, 1453, 1249, 908, 731, 649 $cm^{-1}$; $^1H$ NMR (360 MHz, $CDCl_3$) δ 7.32-7.13 (7H, m, Ar**H**), 6.75 (2H, d, *J* = 8.7 Hz, Ar**H**), 4.52 (1H, d, *J* = 14.6 Hz, NC**H**$_2$Ar), 4.47 (1H, d, *J* = 14.6 Hz, NC**H**$_2$Ar), 3.79 (3H, s, OC**H**$_3$), 3.65-3.62 (1H, m, C**H**$CH_3$), 2.90-2.85 (2H, m, $CH_2$C**H**$_2$N), 2.74-2.73 (1H, m, C**H**C=O), 1.61 (3H, d, *J* = 7.4 Hz, C**H**$_3$CH), 1.53-1.46 (4H, m, C**H**$_2CH_2$N and $CH_3$C**H**$_2$COH), 1.26 (1H, s, O**H**), 0.87 (3H, t, *J* = 7.4 Hz, C**H**$_3CH_2$COH); $^{13}C$ NMR (62.9 MHz, $CDCl_3$) δ 170.1 (C), 158.1 (C), 142.3 (C), 136.9 (C), 129.9 (2 x CH), 128.5 (2 x CH), 128.4 (2 x CH), 127.3 (CH), 113.6 (2 x CH), 72.8 (C), 57.9 (CH), 55.2 ($CH_3$), 50.2 ($CH_2$), 43.0 (CH), 37.8 ($CH_3$), 33.5 ($CH_2$), 29.3 ($CH_2$), 23.5 ($CH_2$),

7.1 ($CH_3$); HRMS (ES) Exact mass calcd for $C_{23}H_{30}NO_3$ $[M+H]^+$: 368.2220, found: 368.2217.

**1-Benzyl-4-hydroxy-4-phenyl-3-(1-phenyl-ethyl)-piperidin-2-one (194ha and 194hb).**

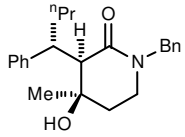



General Procedure D was followed using substrate **192** (148 mg, 0.40 mmol) for a reaction time of 28 h and the reaction mixture was subjected to Workup B followed by purification by column chromatography (20% EtOAc/hexane) to give a 8:5 mixture of two diastereomers and then recolumned (2% $Et_2O/CH_2Cl_2$) to give the minor diastereomeric product **194hb** (28 mg, 18%) as a white solid, followed by the major diastereomeric product **194ha** (37 mg, 24%) as an off-white solid.

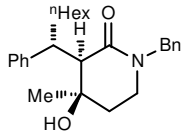
Data for **194hb**: $R_f$ = 0.29 (20% EtOAc/hexane); m.p. 166-168 °C; IR ($CHCl_3$) 3584 (OH), 2252, 1632 (C=O), 1494, 1450, 1352, 1092, 908, 731, 650 $cm^{-1}$; $^1H$ NMR (360 MHz, $CDCl_3$) δ 7.46-7.13 (15H, m, Ar**H**), 4.76 (1H, d, *J* = 14.7 Hz, NC**H**$_2$Ar), 4.57 (1H, d, *J* = 14.7 Hz, NC**H**$_2$Ar), 3.56-3.46 (2H, m, $CH_2$C**H**$_2$N and C**H**$CH_3$), 3.31 (1H, app d, *J* = 2.4 Hz, C**H**C=O), 2.97-2.91 (1H, m, $CH_2$C**H**$_2$N), 2.27-2.19 (1H, m, C**H**$_2CH_2$N), 2.05-1.98 (1H, m, C**H**$_2CH_2$N), 1.89 (1H, s, O**H**), 1.39 (3H, d, *J* = 7.4 Hz, C**H**$_3$CH); $^{13}C$ NMR (62.9 MHz, $CDCl_3$) δ 169.8 (C), 147.5 (C), 145.6 (C), 137.0 (C), 128.5, 128.3, 128.0, 127.5, 127.3, 126.0 and 125.0 (15 x CH), 75.9 (C), 57.9 (CH), 50.8 ($CH_2$), 43.7 ($CH_2$), 37.3 (CH), 35.8 ($CH_2$), 19.3 ($CH_3$); HRMS (EI) Exact mass calcd for $C_{26}H_{27}NO_2$ $[M]^+$: 385.2036, found: 385.2034.

Data for **194ha**: $R_f$ = 0.28 (20% EtOAc/hexane); m.p. 182-184 °C; IR ($CHCl_3$) 3547 (OH), 2928, 2252, 1630 (C=O), 1493, 1452, 1350, 907, 732, 650 $cm^{-1}$; $^1H$ NMR (360 MHz, $CDCl_3$) δ 7.43-7.19 (15H, m, Ar**H**), 4.73 (1H, d, *J* = 14.7 Hz, NC**H**$_2$Ar), 4.56 (1H, d, *J* = 14.7 Hz, NC**H**$_2$Ar), 3.39-3.24 (3H, m, $CH_2$C**H**$_2$N, C**H**$CH_3$ and C**H**C=O), 2.96-2.90 (1H, m, $CH_2$C**H**$_2$N), 2.09 (1H, s, O**H**), 2.09-2.00 (1H, m, C**H**$_2CH_2$N), 1.88-1.82 (1H, m, C**H**$_2CH_2$N), 1.69 (3H, d, *J* = 7.3 Hz, C**H**$_3$CH); $^{13}C$ NMR (62.9 MHz, $CDCl_3$) δ 170.1 (C), 146.2 (C), 144.6 (C), 137.0 (C), 129.4 (2 x CH), 128.7 (2 x CH), 128.6 (2 x CH), 128.4 (2 x CH), 127.8 (CH), 127.2 (CH), 127.1 (CH), 126.9

(CH), 124.6 (2 x CH), 76.1 (C), 56.9 (CH), 50.4 ($CH_2$), 43.5 ($CH_2$), 39.3 (CH), 36.7 ($CH_2$), 24.1 ($CH_3$); HRMS (ES) Exact mass calcd for $C_{26}H_{28}NO_2$ $[M+H]^+$: 386.2115, found: 386.2110.

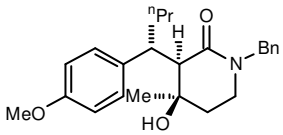



**(±)-(3*R*,4*R*)-1-Benzyl-4-hydroxy-4-methyl-3-[(*R*)-1-phenylbutyl]piperidin-2-one (195a)**. The title compound was prepared according to General Procedure E from **173** (61 mg, 0.20 mmol) for a reaction time of 19 h followed by Workup B and purification by column chromatography (30% EtOAc/hexane) to give a white solid (41 mg, 58%). $R_f$ = 0.18 (30% EtOAc/hexane); m.p. 133-135 °C; IR ($CHCl_3$) 3583 (OH), 2959, 1629 (C=O), 1495, 1453, 1380, 1265, 1145, 1029, 910 $cm^{-1}$; $^1H$ NMR (360 MHz, $CDCl_3$) δ 7.46 (2H, d, *J* = 8.3 Hz, Ar**H**), 7.33-7.29 (7H, m, Ar**H**), 7.20 (1H, t, *J* = 7.3 Hz, Ar**H**), 4.73 (1H, d, *J* = 14.4 Hz, NC**H**$_2$Ar), 4.54 (1H, d, *J* = 14.4 Hz, NC**H**$_2$Ar), 3.35 (1H, ddd, *J* = 12.4, 6.7, 4.0 Hz, $CH_2$C**H**$_2$N), 3.18 (1H, ddd, *J* = 11.7, 4.2, 4.0 Hz, C**H**$CH_2CH_2CH_3$), 3.06 (1H, ddd, J = 12.4, 9.4, 6.3 Hz, $CH_2$C**H**$_2$N), 2.83 (1H, app dd, *J* = 4.2, 1.6 Hz, C**H**C=O), 2.06-1.87 (2H, m, C**H**$_2$), 1.68 (1H, dddd, *J* = 12.2, 6.0, 4.0, 1.7 Hz, $CH_3CH_2$C**H**$_2$), 1.59-1.50 (1H, m, C**H**$_2$), 1.44 (1H, s, O**H**), 1.23 (3H, s, C**H**$_3$COH), 1.11-1.01 (2H, m, $CH_3$C**H**$_2$), 0.82 (3H, t, *J* = 7.3 Hz, C**H**$_3CH_2$); $^{13}C$ NMR (62.9 MHz, $CDCl_3$) δ 170.2 (C), 146.4 (C), 137.1 (C), 128.6 (2 x CH), 128.5 (4 x CH), 128.5 (2 x CH), 127.4 (CH), 126.2 (CH), 71.3 (C), 59.8 (CH), 50.1 ($CH_2$), 44.0 (CH), 43.4 ($CH_2$), 36.6 ($CH_2$), 32.2 ($CH_2$), 28.4 ($CH_3$), 21.1 ($CH_2$), 14.0 ($CH_3$); HRMS (ES) Exact mass calcd for $C_{23}H_{30}NO_2$ $[M+H]^+$: 352.2271, found: 352.2269.

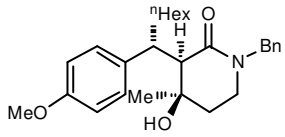



**(±)-(3*R*,4*R*)-1-Benzyl-4-hydroxy-4-methyl-3-[(*R*)-1-phenylheptyl]piperidin-2-one (195b)**. The title compound was prepared according to General Procedure F from **173** (61 mg, 0.20 mmol) for a reaction time of 14 h followed by Workup A and purification by column chromatography (20% EtOAc/hexane→30% EtOAc/hexane) to give an off-white solid (59 mg, 75%). $R_f$ = 0.18 (30% EtOAc/hexane); m.p. 122-124 °C; IR ($CHCl_3$) 3583 (OH), 2928, 1632 (C=O), 1495, 1453, 1380, 908, 733, 651 $cm^{-1}$; $^1H$ NMR (360 MHz, $CDCl_3$) δ 7.45 (2H, dd, *J* = 7.9, 1.2 Hz, Ar**H**), 7.33-7.28 (7H, m, Ar**H**), 7.20 (1H, t, *J* = 7.3 Hz, Ar**H**), 4.76 (1H, d, *J* = 14.4 Hz, NC**H**$_2$Ar), 4.50 (1H, d, *J* = 14.4

Hz, NC**H**$_2$Ar), 3.35 (1H, ddd, *J* = 12.4, 6.7, 4.1 Hz, CH$_2$C**H**$_2$N), 3.16 (1H, ddd, *J* = 11.7, 4.3, 4.1 Hz, C**H**CH$_2$), 3.06 (1H, ddd, *J* = 12.4, 9.4, 6.3 Hz, CH$_2$C**H**$_2$N), 2.83 (1H, app dd, *J* = 4.3, 1.8 Hz, C**H**C=O), 2.06-1.87 (2H, m, C**H**$_2$), 1.68 (1H, dddd, *J* = 13.2, 6.1, 4.1, 1.8 Hz, CHC**H**$_2$CH$_2$), 1.63-1.53 (1H, m, C**H**$_2$), 1.35 (1H, s, O**H**), 1.27-1.14 (6H, m, CH$_3$CH$_2$C**H**$_2$C**H**$_2$C**H**$_2$), 1.23 (3H, s, C**H**$_3$COH), 1.06-0.98 (2H, m, CH$_3$C**H**$_2$), 0.84 (3H, t, *J* = 7.0 Hz, C**H**$_3$CH$_2$); $^{13}$C NMR (62.9 MHz, CDCl$_3$) δ 170.2 (C), 146.4 (C), 137.1 (C), 128.7 (2 x CH), 128.5 (4 x CH), 128.5 (2 x CH), 127.4 (CH), 126.2 (CH), 71.3 (C), 59.8 (CH), 50.1 (CH$_2$), 44.2 (CH), 43.4 (CH$_2$), 34.3 (CH$_2$), 32.3 (CH$_2$), 31.7 (CH$_2$), 29.3 (CH$_2$), 28.4 (CH$_3$), 27.9 (CH$_2$), 22.6 (CH$_2$), 14.0 (CH$_3$); HRMS (ES) Exact mass calcd for $C_{26}H_{36}NO_2$ [M+H]$^+$: 394.2741 found: 394.2735.



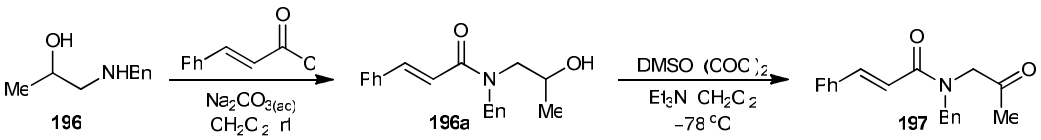

**(±)-(3*R*,4*R*)-1-Benzyl-4-hydroxy-3-[(*R*)-1-(4-methoxyphenyl)butyl]-4-methylpiperidin-2-one (195c)**. The title compound was prepared according to General Procedure E from **181** (67 mg, 0.20 mmol) for a reaction time of 19 h followed by Workup B and purification by column chromatography (40% EtOAc/hexane) to give a white solid (47 mg, 62%). $R_f$ = 0.28 (40% EtOAc/hexane); m.p. 138-140 °C; IR (CHCl$_3$) 3483 (OH), 2959, 1633 (C=O), 1511, 1454, 1380, 1247, 1178, 1045, 909 cm$^{-1}$; $^1$H NMR (360 MHz, CDCl$_3$) δ 7.37-7.28 (7H, m, Ar**H**), 6.85 (2H, d, *J* = 8.6 Hz, Ar**H**), 4.72 (1H, d, *J* = 14.4 Hz, NC**H**$_2$Ar), 4.52 (1H, d, *J* = 14.4 Hz, NC**H**$_2$Ar), 3.79 (3H, s, OC**H**$_3$), 3.34 (1H, ddd, *J* = 12.2, 6.6, 4.1 Hz, CH$_2$C**H**$_2$N), 3.15 (1H, ddd, *J* = 11.6, 4.2, 4.0 Hz, C**H**CH$_2$CH$_2$CH$_3$), 3.05 (1H, ddd, *J* = 12.2, 9.3, 6.4 Hz, CH$_2$C**H**$_2$N), 2.79 (1H, app dd, *J* = 4.2, 1.5 Hz, C**H**C=O), 2.05-1.83 (2H, m, C**H**$_2$), 1.70-1.64 (1H, m, C**H**$_2$), 1.59-1.48 (2H, m, C**H**$_2$ and O**H**), 1.22 (3H, s, C**H**$_3$COH), 1.06 (2H, app sextet, app *J* = 7.5 Hz, CH$_2$C**H**$_2$CH$_3$), 0.82 (3H, t, *J* = 7.2 Hz, C**H**$_3$CH$_2$); $^{13}$C NMR (62.9 MHz, CDCl$_3$) δ 170.4 (C), 158.0 (C), 138.0 (C), 137.1 (C), 129.6 (2 x CH), 128.5 (2 x CH), 128.4 (2 x CH), 127.4 (CH), 113.9 (2 x CH), 71.3 (C), 59.8 (CH), 55.2 (CH$_3$), 50.1 (CH$_2$), 43.4 (CH$_2$), 43.2 (CH), 36.8 (CH$_2$), 32.4 (CH$_2$), 28.4 (CH$_3$), 21.0 (CH$_2$), 14.0 (CH$_3$); HRMS (ES) Exact mass calcd for $C_{24}H_{32}NO_3$ [M+H]$^+$: 382.2377, found: 382.2377.



**(±)-(3*R*,4*R*)-1-Benzyl-4-hydroxy-3-[(*R*)-1-(4-methoxyphenyl)heptyl]-4-methylpiperidin-2-one (195d)**. The title compound was prepared according to a slight modification of General Procedure F (an extra 1 equiv of $Hex_3Al$ added after 18 h) from **181** (67 mg, 0.20 mmol) for a reaction time of 22 h followed by Workup A and purification by column chromatography (40% EtOAc/hexane) to give a white solid (51 mg, 61%). $R_f$ = 0.12 (30% EtOAc/hexane); m.p. 110-112 °C; IR ($CHCl_3$) 3210 (OH), 2929, 1631 (C=O), 1510, 1265, 910, 733, 650 $cm^{-1}$; $^1H$ NMR (360 MHz, $CDCl_3$) δ 7.36-7.28 (7H, m, Ar**H**), 6.86 (2H, d, *J* = 8.7 Hz, Ar**H**), 4.76 (1H, d, *J* = 14.4 Hz, NC**H**$_2$Ar), 4.49 (1H, d, *J* = 14.4 Hz, NC**H**$_2$Ar), 3.80 (3H, s, OC**H**$_3$), 3.34 (1H, ddd, *J* = 12.3, 6.8, 4.2 Hz, $CH_2$C**H**$_2$N), 3.15-3.01 (2H, m, $CH_2$C**H**$_2$N and C**H**$CH_2CH_2$), 2.79 (1H, app dd, *J* = 4.7, 1.5 Hz, C**H**C=O), 2.00 (1H, ddd, *J* = 13.4, 9.1, 6.8 Hz, C**H**$_2CH_2$N), 1.94-1.83 (1H, m, C**H**$_2$), 1.71-1.53 (2H, m, C**H**$_2$), 1.34 (1H, s, O**H**), 1.27-1.13 (6H, m, $CH_3CH_2$C**H**$_2$C**H**$_2$C**H**$_2$), 1.23 (3H, s, C**H**$_3$COH), 1.07-0.99 (2H, m, C**H**$_2CH_3$), 0.84 (3H, t, *J* = 7.0 Hz, C**H**$_3CH_2$); $^{13}C$ NMR (62.9 MHz, $CDCl_3$) δ 170.4 (C), 158.0 (C), 137.9 (C), 137.1 (C), 129.6 (2 x CH), 128.6 (2 x CH), 128.5 (2 x CH), 127.4 (CH), 114.0 (2 x CH), 71.4 (C), 59.9 (CH), 55.2 ($CH_3$), 50.1 ($CH_2$), 43.5 (CH), 43.4 ($CH_2$), 34.6 ($CH_2$), 32.5 ($CH_2$), 31.8 ($CH_2$), 29.3 ($CH_2$), 28.5 ($CH_3$), 27.9 ($CH_2$), 22.6 ($CH_2$), 14.0 ($CH_3$); HRMS (ES) Exact mass calcd for $C_{27}H_{38}NO_3$ $[M+H]^+$: 424.2846, found: 424.2848.

### 6.1.3 Expansion of Substrate Scope

***N*-Benzyl-*N*-(2-oxopropyl)-3-phenylacrylamide (197)**.



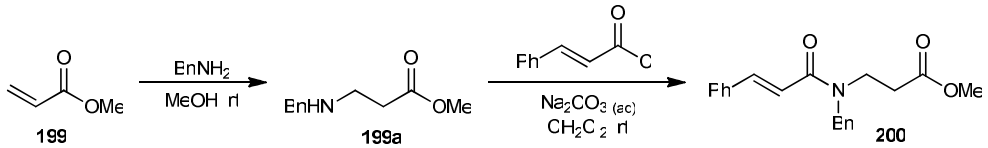

Saturated aqueous $Na_2CO_3$ solution (40 mL) and cinnamoyl chloride (3.14 g, 18.9 mmol) were added to a solution of 1-benzylaminopropan-2-ol (2.57 g, 15.6 mmol) in $CH_2Cl_2$ (50 mL). The mixture was stirred at room temperature for 16 h and then partitioned between saturated aqueous $NaHCO_3$ solution and $CH_2Cl_2$. The aqueous layer was separated and extracted with $CH_2Cl_2$ (x 3), and the combined organic layers were washed with 10% HCl solution (x 1), dried ($MgSO_4$) and concentrated *in*

*vacuo*. Purification of the residue by column chromatography (50-60% EtOAc/petrol) gave *N-Benzyl-N-(2-hydroxypropyl)-3-phenylacrylamide* (**196a**) as a colourless oil (3.54 g, 77%) as a 2:1 mixture of rotamers. $R_f$ = 0.12 (40% EtOAc/petrol); IR ($CHCl_3$) 3376, 2973, 2252, 1797 (C=O), 1646 (C=C), 1596, 1472, 1212, 907, 732 $cm^{-1}$; $^1H$ NMR (360 MHz, $CDCl_3$) (Major rotamer) δ 7.80 (1H, d, *J* = 15.3 Hz, PhC**H**=), 7.52-7.23 (10H, m, Ar**H**), 6.82 (1H, d, *J* = 15.3 Hz, PhCH=C**H**), 4.99-4.63 (2H, m, C**H**$_2$Ph), 4.19 (1H, s, O**H**), 4.16-4.07 (1H, m, C**H**OH), 3.71 (1H, dd, *J* = 8.4, 14.2 Hz, CHOHC**H**$_2$N), 3.31 (1H, dd, *J* = 2.3, 14.2 Hz, CHOHC**H**$_2$N), 1.20 (3H, d, *J* = 6.3 Hz, C**H**$_3$CHOH); (Minor rotamer) δ 7.76 (1H, d, *J* = 15.3 Hz, PhC**H=**), 7.52-7.23 (10H, m, Ar**H**), 7.10 (1H, d, *J* = 15.3 Hz, PhCH=C**H**), 4.99-4.63 (2H, m, C**H**$_2$Ph), 4.19 (1H, s, OH), 4.16-4.07 (1H, m, C**H**OH), 3.48 (1H, dd, *J* = 8.9, 15.2 Hz, CHOHC**H**$_2$N), 3.30-3.24 (1H, m, CHOHC**H**$_2$N), 1.20 (3H, d, *J* = 6.3 Hz, C**H**$_3$CHOH); $^{13}C$ NMR (62.9 MHz, $CDCl_3$) (Mixture of rotamers – not fully assigned) δ 169.3 (C), 144.2 (CH), 136.5 (C), 134.9 (C), 129.8 (CH), 129.0 (CH), 128.7 (2 x CH), 128.6 (2 x CH), 127.9 (2 x CH), 127.8 (2 x CH), 116.8 (CH), 67.6 (CH), 55.6 ($CH_2$), 53.0 ($CH_2$), 21.5 ($CH_3$); HRMS (EI) Exact mass calcd for $C_{19}H_{21}NO_2$ $[M]^+$: 295.1567, found: 295.1566.

A solution of oxalyl chloride (0.86 g, 6.77 mmol) in $CH_2Cl_2$ (15 mL) was cooled to –78 $^oC$ and stirred for 5 min. DMSO (1.06 g, 13.56 mmol) was added slowly as a solution in $CH_2Cl_2$ (3 mL). After 15 min *N-benzyl-N-(2-hydroxypropyl)-3-phenylacrylamide* (**196a**) (1.00 g, 3.39 mmol) was added as a solution in $CH_2Cl_2$ (7 mL) and the reaction mixture was stirred for a further 15 min before adding $Et_3N$ (1.37 g, 13.56 mmol). After 5 min the reaction mixture was warmed to rt and water (20 mL) was added. After 1 h the organic layer was separated and the aqueous layer was extracted with $CH_2Cl_2$ (2 x 30 mL). The combined organic layers were dried ($MgSO_4$) and the filtrate was concentrated *in vacuo*. Purification of the crude residue by silica column chromatography (45% EtOAc/petrol) gave the title compound as a colourless oil (1.63 mmol, 48%). as a 5:1 mixture of rotamers. $R_f$ = 0.15 (40% EtOAc/petrol); IR ($CHCl_3$) 3031, 2252, 1732 (C=O), 1650 (C=C), 1606, 1434, 1204, 907, 731, 650 $cm^{-1}$; $^1H$ NMR (360 MHz, $CDCl_3$) (Major rotamer) δ 7.78 (1H, d, *J* = 15.4 Hz, PhC**H**=), 7.49-7.24 (10H, m, Ar**H**), 6.92 (1H, d, *J* = 15.4 Hz, PhCH=C**H**),

4.76 (2H, s, C**H**$_2$Ph), 4.22 (2H, s, O=CC**H**$_2$N), 2.17 (3H, s, C**H**$_3$C=O); (Minor rotamer) δ 7.78 (1H, d, *J* = 15.4 Hz, PhC**H**=), 7.49-7.24 (7H, m, Ar**H**), 6.57 (1H, d, *J* = 15.4 Hz, PhCH=C**H**), 4.76 (2H, s, C**H**$_2$Ph), 4.15 (2H, s, O=CC**H**$_2$N), 2.10 (3H, s, C**H**$_3$C=O); $^{13}$C NMR (62.9 MHz, $CDCl_3$) (Mixture of rotamers – not fully assigned) δ 203.1 (C), 167.2 (C), 144.0 (CH), 136.3 (C), 134.9 (C), 129.7 (2 x CH), 128.9 (2 x CH), 128.7 (2 x CH), 127.8 (2 x CH), 126.7 (2 x CH), 116.4 (CH), 55.7 ($CH_2$), 52.3 ($CH_2$), 27.3 ($CH_3$); HRMS (EI) Exact mass calcd for $C_{19}H_{19}NO_2$ $[M]^+$: 293.1410, found: 293.1411.

**3-Benzyl-(*E*)-(3-phenylacryloyl)aminopropionic acid methyl ester (200)**.

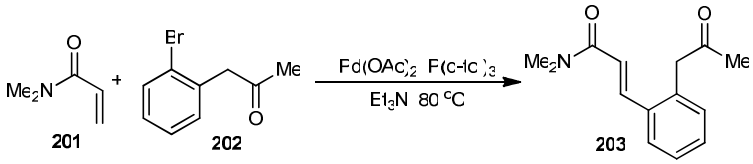



Methyl acrylate (991 μL, 11 mmol) was added to a stirred solution of benzylamine (1.09 mL, 10 mmol) in MeOH (8 mL). The reaction mixture was stirred at room temperature for 46 h then concentrated *in vacuo* to afford **199a** as a yellow oil (1.60 g), which was used directly in the next step.

Cinnamoyl chloride (2.01 g, 12.1 mmol) was added to a mixture of the amine **199a** (10 mmol) in $CH_2Cl_2$ (25 mL) and saturated aqueous $Na_2CO_3$ solution (25 mL) at room temperature. After 24 h the reaction was partitioned between saturated aqueous $NaHCO_3$ solution and $CH_2Cl_2$. The aqueous layer was separated and extracted with $CH_2Cl_2$ (x 3), and the combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo* to afford a yellow residue. Purification by silica column chromatography (30% EtOAc/hexane) gave the title compound as a white solid (2.71 g, 84%) as a 3:2 mixture of rotamers. $R_f$ = 0.31 (30% EtOAc/petrol); m.p. 58-60 °C; IR ($CHCl_3$) 3439, 2953, 1734 (C=O), 1647 (C=C), 1604, 1438, 1203, 908, 732, 650 cm$^{-1}$; $^1$H NMR (360 MHz, $CDCl_3$) (Major rotamer) δ 7.85-7.75 (1H, m, PhC**H**=), 7.58-7.23 (10H, m, Ar**H**), 6.83 (1H, d, *J* = 15.4 Hz, PhCH=C**H**), 4.78 (2H, s, C**H**$_2$Ph), 3.75 (2H, t, *J* = 7.0 Hz, $CH_2$C**H**$_2$N), 3.66 (3H, s, OC**H**$_3$), 2.73 (2H, t, *J* = 6.8 Hz, C**H**$_2$$CH_2$N; (Minor rotamer) δ 7.85-7.75 (1H, m, PhC**H**=), 7.58-7.23 (10H, m, Ar**H**), 7.00 (1H, d, *J* = 15.3 Hz, PhCH=C**H**), 4.75 (2H, s, C**H**$_2$Ph), 3.75 (2H, t, *J* = 7.0 Hz, $CH_2$C**H**$_2$N), 3.66 (3H, s, OC**H**$_3$), 2.62 (2H, t, *J* = 6.7 Hz, C**H**$_2$$CH_2$N); $^{13}$C NMR (62.9

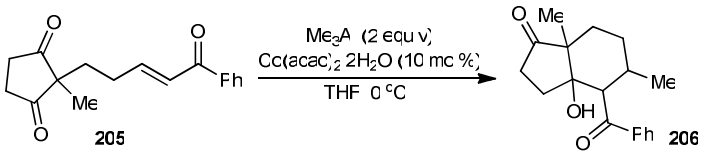
MHz, $CDCl_3$) (Mixture of rotamers – not fully assigned) δ 172.5 (C), 167.1 (C), 166.6 (C), 143.8 (CH), 143.3 (CH), 137.3 (C), 137.0 (C), 135.0 (C), 129.6 (CH), 128.9 (CH), 128.7 (CH), 128.0 (CH), 127.8 (CH), 127.6 (CH), 127.4 (CH), 126.4 (CH), 117.1 (CH), 116.7 (CH), 52.2 ($CH_2$), 51.6 ($CH_3$), 49.1 ($CH_2$), 43.4 ($CH_2$), 42.8 ($CH_2$), 33.9 ($CH_2$), 32.6 ($CH_2$); HRMS (ES) Exact mass calcd for $C_{20}H_{22}NO_3$ $[M+H]^+$: 324.1594 found 324.1595.

**(*E*)-*N*,*N*-Dimethyl-3-[2-(2-oxopropyl)phenyl]acrylamide (203)**.




A solution of 2-bromophenylacetone (1.06 g, 5.0 mmol), *N,N*-dimethylacrylamide (743 mg, 7.5 mmol), $Pd(OAc)_2$ (56 mg, 0.25 mmol) and tri-*o*-tolylphosphine (122 mg, 0.40 mmol) in $Et_3N$ (3.5 mL) was stirred under reflux at 80 °C for 23 h. The reaction residue was partitioned between $CH_2Cl_2$ and 10 % HCl solution and the aqueous layer was separated and extracted with $CH_2Cl_2$ (x 2). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by silica column chromatography (10% acetone/$CH_2Cl_2$→20% acetone/$CH_2Cl_2$) gave the title compound as a pale yellow solid (995 mg, 86%). $R_f$ = 0.20 (10% acetone/$CH_2Cl_2$); m.p. 78-80 °C; IR ($CHCl_3$) 3430, 2932, 1720 (C=O), 1647 (C=C), 1606, 1493, 1398, 1145, 761, 725 $cm^{-1}$; $^1H$ NMR (360 MHz, $CDCl_3$) δ 7.75 (1H, d, *J* = 15.2 Hz, ArC**H**=), 7.61-7.58 (1H, m, Ar**H**), 7.29-7.25 (2H, m, Ar**H**), 7.15-7.13 (1H, m, Ar**H**), 6.82 (1H, d, *J* = 15.2 Hz, ArCH=C**H**), 3.86 (2H, s, C**H**$_2$), 3.09 (3H, s, N(C**H**$_3$)$_2$), 3.01 (3H, s, N(C**H**$_3$)$_2$), 2.17 (3H, s, COC**H**$_3$); $^{13}C$ NMR (62.9 MHz, $CDCl_3$) δ 204.6 (C), 165.6 (C), 138.5 (CH), 134.3 (C), 133.2 (C), 130.5 (CH), 128.8 (CH), 126.9 (CH), 126.1 (CH), 119.3 (CH), 47.3 ($CH_2$), 36.6 ($CH_3$), 35.1 ($CH_3$), 29.1 ($CH_3$); HRMS (EI) Exact mass calcd for $C_{14}H_{17}NO_2$ $[M]^+$: 231.1254, found: 231.1254.

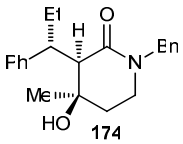
**4-Benzoyl-3a-hydroxy-5,7a-dimethyloctahydroinden-1-one (206)**.



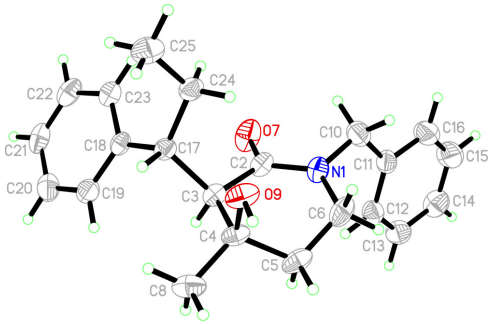

The title compound was prepared according to General Procedure D from **205** (54 mg, 0.20 mmol) for a reaction time of 17 h followed by Workup C. Purification by column chromatography (10% EtOAc/hexane→20% EtOAc/hexane) gave the title compound as a white solid (44 mg, 77%). $R_f$ = 0.26 (20% EtOAc/hexane); m.p. 125-127 °C; IR ($CHCl_3$) 3473 (OH), 2956, 1734, 1655 (C=O), 1448, 1354, 1227, 1059, 891, 690 $cm^{-1}$; $^1H$ NMR (360 MHz, $CDCl_3$) δ 7.94 (2H, d, *J* = 8.0 Hz, Ar**H**), 7.65 (1H, t, *J* = 7.4 Hz, Ar**H**), 7.52 (2H, t, *J* = 7.9 Hz, Ar**H**), 5.06 (1H, s, O**H**), 3.05 (1H, d, *J* = 11.1 Hz, C**H**C=OPh), 2.56 (1H, ddd, *J* = 19.6, 10.6, 1.5 Hz, C$\mathbf{H}_2$C=O), 2.26 (1H, app dd, *J* = 19.6, 10.0 Hz, C$\mathbf{H}_2$C=O), 2.19-1.98 (3H, m, C$\mathbf{H}_2$$CH_2$C=O and C**H**$CH_3$), 1.63-1.50 (3H, m, C$\mathbf{H}_2$C$\mathbf{H}_2$$CHCH_3$), 1.10-0.98 (1H, m, $CH_2$C$\mathbf{H}_2$$CHCH_3$), 1.06 (3H, s, CC$\mathbf{H}_3$), 0.71 (3H, d, *J* = 6.6 Hz, CHC$\mathbf{H}_3$); $^{13}C$ NMR (62.9 MHz, $CDCl_3$) δ 218.0 (C), 207.8 (C), 138.7 (C), 134.3 (CH), 129.1 (2 x CH), 128.1 (2 x CH), 78.3 (C), 53.5 (C), 53.2 (CH), 34.6 ($CH_2$), 32.0 (CH), 31.6 ($CH_2$), 31.4 ($CH_2$), 28.0 ($CH_2$), 20.5 ($CH_3$), 19.4 ($CH_3$); HRMS (ES) Exact mass calcd for $C_{18}H_{23}O_3$ $[M+H]^+$: 284.1642, found: 287.1642.

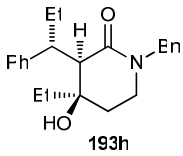
**Stereochemical Determinations**

- The relative stereochemistries of **173** and **193h** were determined by X-ray crystallography.

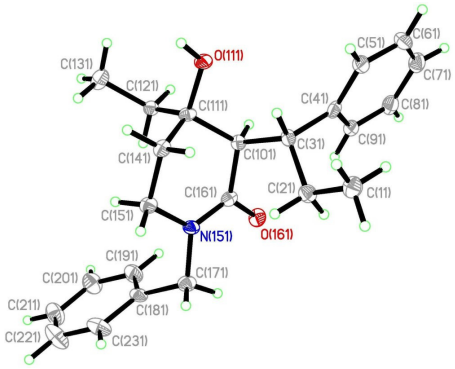



174




193h

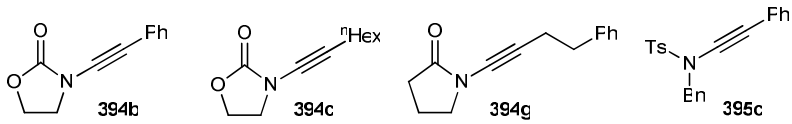



NE Due to the weakly diffracting and twinned nature of the crystals for **193h** the X-ray crystallographic data were not of the highest quality but there is no doubt about the composition and stereochemistry of **174**

- The relative stereochemistries of the remaining products were assigned by analogy.

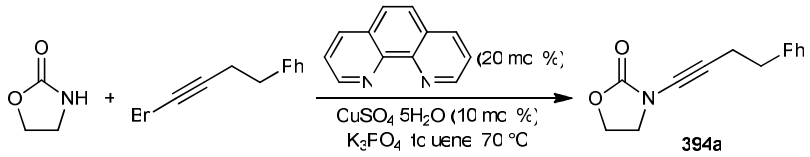
## 6.2 Rhodium-Catalysed Carbometallation of Ynamides to Access Multisubstituted Enamides

### 6.2.1 Preparation of Ynamide Starting Materials




Ynamides **394b**, **394c**, **394g**, and **395c** were prepared by Benoit Gourdet as described previously.[160]

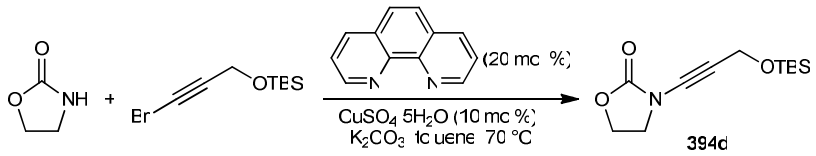
**3-(4-Phenylbut-1-ynyl)oxazolidin-2-one (394a)**




Following a slight modification of the procedure of Hsung and co-workers,[162a] a mixture of 1-bromo-4-phenyl-1-butyne (1.93 g, 9.24 mmol), 2-oxazolidinone (731 mg, 8.40 mmol), $K_3PO_4$ (3.57 g, 16.8 mmol), $CuSO_4 \cdot 5H_2O$ (210 mg, 0.84 mmol), and 1,10-phenanthroline (303 mg, 1.68 mmol) in toluene (20 mL) was heated at 70 °C for 40 h. After cooling to room temperature, the mixture was filtered through a short pad of silica gel using $CH_2Cl_2$ (40 mL) as the eluent, and the filtrate was concentrated *in vacuo*. Purification of the residue by column chromatography (20% EtOAc/hexane→30%EtOAc/hexane) gave the *ynamide* **394a** (1.11 g, 62%) as a pale yellow solid that displayed identical spectroscopic data to those reported previously.[160] $R_f$ = 0.46 (50% EtOAc/hexane); IR ($CHCl_3$) 2956, 2929, 2304 (C≡C), 1773 (C=O), 1653, 1481, 1419, 1265, 1115, 1040, 738 $cm^{-1}$; $^1H$ NMR (360 MHz, $CDCl_3$) δ 7.33-7.29 (2H, m, Ar**H**), 7.24-7.20 (3H, m, Ar**H**), 4.42-4.38 (2H, m, C**H**$_2$O), 3.85-3.81 (2H, m, C**H**$_2$N), 2.86 (2H, t, *J* = 7.6 Hz, ≡CC**H**$_2$), 2.61 (2H, t, *J* = 7.6 Hz, C**H**$_2$Ph); $^{13}C$ NMR (62.9 MHz, $CDCl_3$) δ 156.5 (C), 140.4 (C), 128.4 (2 x

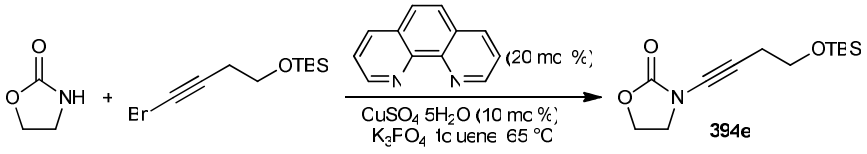
CH), 128.3 (2 x CH), 126.2 (C), 70.7 (C), 70.3 (C), 62.8 ($CH_2$), 46.8 ($CH_2$), 35.1 ($CH_2$), 20.6 ($CH_2$).

**3-[3-(*tert*-Butyldimethylsilyloxy)prop-1-ynyl]oxazolidin-2-one (394d)**




Following a slight modification of the procedure of Hsung and co-workers,[162a] a mixture of 1-bromo-3-*tert*-butyldimethylsilyloxyprop-1-yne (4.51 g, 18.1 mmol), 2-oxazolidinone (1.44 g, 16.5 mmol), $K_2CO_3$ (4.56 g, 33.0 mmol), $CuSO_4{\cdot}5H_2O$ (412 mg, 1.65 mmol), 1,10-phenanthroline (595 mg, 3.30 mmol) in toluene (30 mL) was heated at 70 °C for 40 h. After cooling to room temperature, the mixture was filtered through a short pad of silica gel using $CH_2Cl_2$ (100 mL) as the eluent, and the filtrate was concentrated *in vacuo*. Purification of the residue by column chromatography (30% EtOAc/hexane) gave the *ynamide* **394d** (2.78 g, 66%) as a white solid that displayed spectroscopic data consistent with those observed previously.[162c] $R_f$ = 0.20 (30% EtOAc/hexane); m.p. 68-70 °C; IR ($CHCl_3$) 2930, 2858, 2253 (C≡C), 1773 (C=O), 1480, 1422, 1209, 1114, 907, 837 $cm^{-1}$; $^1H$ NMR (360 MHz, $CDCl_3$) δ 4.46 (2H, s, C**H**$_2$OSi), 4.46-4.41 (2H, m, C**H**$_2$O), 3.93-3.89 (2H, m, C**H**$_2$N), 0.91 (9H, s, C(C**H**$_3$)$_3$), 0.12 (6H, s, Si(C**H**$_3$)$_2$; $^{13}C$ NMR (62.9 MHz, $CDCl_3$) δ 156.0 (C), 74.7 (C), 70.3 (C), 62.9 ($CH_2$), 51.6 ($CH_2$), 46.6 ($CH_2$), 25.8 (3 x $CH_3$), 18.2 (C), -5.1 (2 x $CH_3$); HRMS (ES) Exact mass calcd for $C_{12}H_{22}NO_3Si$ [M+H$^+$]: 256.1363, found: 256.1363.

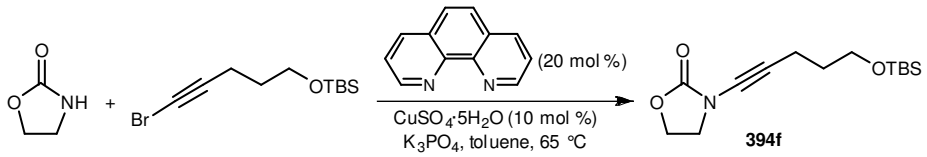
**3-[4-(*tert*-Butyldimethylsilyloxy)but-1-ynyl]oxazolidin-2-one (394e)**




Following the procedure of Hsung and co-workers,[162a] a mixture of 1-bromo-4-*tert*-butyldimethylsilyloxy-1-butyne (3.93 g, 14.9 mmol), 2-oxazolidinone (1.18 g, 13.5 mmol), $K_3PO_4$ (5.73 g, 27.0 mmol), $CuSO_4{\cdot}5H_2O$ (337 mg, 1.35 mmol), and 1,10-phenanthroline (487 mg, 2.70 mmol) in toluene (30 mL) was heated at 65 °C for 40

h. After cooling to room temperature, the mixture was filtered through a short pad of silica gel using $CH_2Cl_2$ (40 mL) as the eluent, and the filtrate was concentrated *in vacuo*. Purification of the residue by column chromatography (25% EtOAc/hexane) gave the *ynamide* **394e** (1.10 g, 31%) as a colourless oil which displayed spectroscopic data consistent with those observed previously.[160] $R_f$ = 0.21 (25% EtOAc/hexane); IR (film) 2955, 2929, 2253 (C≡C), 1772 (C=O), 1480, 1419, 1256, 1112, 1040, 733 $cm^{-1}$; $^1H$ NMR (250 MHz, $CDCl_3$) δ 4.46-4.39 (2H, m, $NCH_2CH_2O$), 3.91-3.85 (2H, m, $CH_2N$), 3.74 (2H, t, *J* = 7.1 Hz, $CH_2OSi$), 2.53 (2H, t, *J* = 7.1 Hz, $\equiv CCH_2$), 0.90 (9H, s, $SiC(CH_3)_3$), 0.08 (6H, s, $Si(CH_3)_2$); $^{13}C$ NMR (62.9 MHz, $CDCl_3$) δ 156.4 (C), 70.9 (C), 68.0 (C), 62.8 ($CH_2$), 61.8 ($CH_2$), 46.8 ($CH_2$), 25.7 (3 x $CH_3$), 22.6 ($CH_2$), 18.2 (C), –5.4 (2 x $CH_3$).

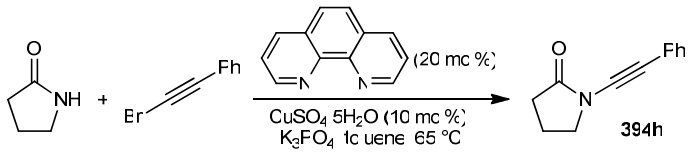
**3-(5-*tert*-Butyldimethylsilyloxypent-1-ynyl)oxazolidin-2-one (394f)**




Following a slight modification of the procedure of Hsung and co-workers,[162a] a mixture of 1-bromo-5-*tert*-butyldimethylsilyloxypent-1-yne (4.66 g, 16.8 mmol), 2-oxazolidinone (1.33 g, 15.3 mmol), $K_3PO_4$ (6.50 g, 30.6 mmol), $CuSO_4{\cdot}5H_2O$ (382 mg, 1.53 mmol), 1,10-phenanthroline (551 mg, 3.06 mmol) in toluene (30 mL) was heated at 65 °C for 40 h. After cooling to room temperature, the mixture was filtered through a short pad of silica gel using $CH_2Cl_2$ (100 mL) as the eluent, and the filtrate was concentrated *in vacuo*. Purification of the residue by column chromatography (25% EtOAc/hexane) gave the *ynamide* **394f** (945 mg, 22%) as a pale yellow oil that displayed spectroscopic data consistent with those observed previously.[162c] $R_f$ = 0.17 (20% EtOAc/hexane); IR (film) 2956, 2929, 2857, 2258 (C≡C), 1770 (C=O), 1481, 1418, 1213, 1114, 911, 733 $cm^{-1}$; $^1H$ NMR (360 MHz, $CDCl_3$) δ 4.41 (2H, dd, *J* = 8.7, 7.3 Hz, $CH_2O$), 3.91-3.81 (2H, m, $CH_2N$), 3.69 (2H, t, *J* = 6.0 Hz, $CH_2CH_2OSi$), 2.44-2.36 (2H, m, $CH_2CH_2CH_2OSi$), 1.79-1.67 (2H, m, $CH_2CH_2CH_2OSi$), 0.90 (9H, s, $C(CH_3)_3$), 0.06 (6H, s, $Si(CH_3)_2$); $^{13}C$ NMR (62.9 MHz, $CDCl_3$) δ 156.6 (C), 70.7 (C), 70.1 (C), 62.7 ($CH_2$), 61.5 ($CH_2$), 46.9

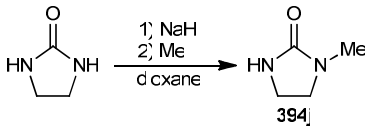
($CH_2$), 31.7 ($CH_2$), 25.9 (3 x $CH_3$), 18.3 (C), 14.8 ($CH_2$), -5.4 (2 x $CH_3$); HRMS (ES) Exact mass calcd for $C_{14}H_{26}NO_3Si$ [M+$H^+$]: 284.1676, found: 284.1674.

**1-Phenylethynylpyrrolidin-2-one (394h)**




Following the procedure of Hsung and co-workers,[162a] a mixture of 1-bromo-2-phenylacetylene (7.97 g, 44.0 mmol), 2-pyrrolidinone (3.40 g, 40.0 mmol), $K_2CO_3$ (11.1 g, 80.0 mmol), $CuSO_4 \cdot 5H_2O$ (998 mg, 4.00 mmol), and 1,10-phenanthroline (1.44 g, 8.00 mmol) in toluene (100 mL) was heated at 65 °C for 40 h. After cooling to room temperature, the mixture was filtered through a short pad of silica gel using $CH_2Cl_2$ (20 mL) as the eluent, and the filtrate was concentrated *in vacuo*. Purification of the residue by column chromatography (25% EtOAc/hexane) gave the *ynamide* **394h** (1.93 g, 35%) as a red oil that displayed identical spectroscopic data to those reported previously.[160] $R_f$ = 0.12 (25% EtOAc/hexane); IR (film) 2955, 2924, 2259 (C≡C), 1759 (C=O), 1481, 1417, 1256, 1233, 1051, 729 $cm^{-1}$; $^1H$ NMR (360 MHz, $CDCl_3$) δ 7.46-7.44 (2H, m, Ar**H**), 7.31-7.27 (3H, m, Ar**H**), 3.78 (2H, dd, *J* = 7.4 Hz, 6.9 Hz, C**H**$_2$N), 2.49 (2H, t, *J* = 8.0 Hz, C**H**$_2$C(O)), 2.18 (2H, quint, *J* = 7.5 Hz, $CH_2C\mathbf{H}_2CH_2$); $^{13}C$ NMR (62.9 MHz, $CDCl_3$) δ 175.7 (C), 131.5 (2 x CH), 128.2 (2 x CH), 127.9 (CH), 122.6 (C), 80.4 (C), 72.5 (C), 50.1 ($CH_2$), 29.7 ($CH_2$), 18.8 ($CH_2$).

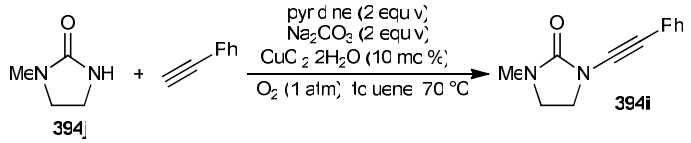
**1-Methylimidazolidin-2-one (394j)[182]**




To a solution of 2-imidazolidinone (6.02 g, 70 mmol) in 1,4-dioxane (80 mL) was added NaH (3.32 g, 82.6 mmol, 60 wt% in paraffin) under an atmosphere of nitrogen with vigorous stirring. The solution was heated to 65 °C and stirred at this temperature for 2 h and then cooled to 0 °C. $CH_3I$ was added slowly *via* syringe pump and the resulting mixture was stirred at rt for 18 h. The mixture was filtered

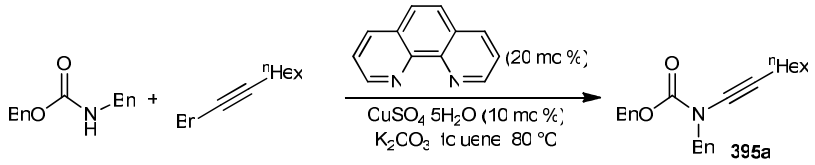
through a celite plug and the filtrate was concentrated *in vacuo*. Purification by silica column chromatography (10% MeOH/$CH_2Cl_2$) gave the title compound as a white solid (1.94 g, 28%) which displayed identical spectroscopic data to those described previously.[182] $R_f$ = 0.44 (10% MeOH/$CH_2Cl_2$); mp = 108-110 °C; $^1$H NMR (360 MHz, $CDCl_3$) δ 4.73 (1H, br s, N**H**), 3.41 (4H, s, C**H**$_2$), 2.79 (3H, s, C**H**$_3$N); $^{13}$C NMR (62.9 MHz, $CDCl_3$) δ 163.3 (C), 47.5 ($CH_2$), 38.0 ($CH_2$), 30.6 ($CH_3$).

**3-Methyl-1-phenylethynylimidazolidin-2-one (394i)**



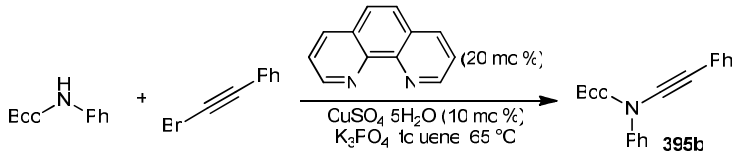

Following a slight modification of the procedure of Stahl and co-workers,[162c] in a three-neck flask, $CuCl_2{\cdot}2H_2O$ (409 mg, 2.16 mmol), $Na_2CO_3$ (2.33 g, 22.0 mmol) and 1-methylimidazolidin-2-one (5.40 g, 54.0 mmol) were combined. The reaction flask was purged with $O_2$ for 15 min. A solution of pyridine (1.74 g, 22.0 mmol) in toluene (100 mL) was then added. A balloon filled with $O_2$ was connected to the flask, and the mixture was heated to 70 °C. A solution of phenylacetylene (1.11 g, 10.8 mmol) in toluene (20 mL) was added to the mixture over 7 h *via* syringe pump. The mixture was stirred at 70 °C for 16 h, cooled to room temperature and then filtered through a short pad of silica gel using $CH_2Cl_2$ (40 mL) as eluent. The filtrate was concentrated *in vacuo* and purification by column chromatography (50% EtOAc/hexane→70%EtOAc/hexane) gave the *ynamide* **394i** (1.24 g, 57%) as a colourless solid that displayed identical spectroscopic data to those reported previously.[162c] $R_f$ = 0.25 (50% EtOAc/hexane); mp = 86-88 °C; IR ($CHCl_3$) 2929, 2277 (C≡C), 1765 (C=O), 1481, 1433, 1256, 1202, 1122, 1040, 731 cm$^{-1}$; $^1$H NMR (360 MHz, $CDCl_3$) δ 7.45-7.42 (2H, m, Ar**H**), 7.29-7.25 (3H, m, Ar**H**), 3.82-3.78 (2H, m, C**H**$_2$N), 3.49-3.45 (2H, m, C**H**$_2$N), 2.88 (3H, s, C**H**$_3$N); $^{13}$C NMR (62.9 MHz, $CDCl_3$) δ 157.5 (C), 131.2 (2 x CH), 128.1 (2 x CH), 127.3 (CH), 123.4 (C), 82.2 (C), 70.0 (C), 44.7 ($CH_2$), 44.4 ($CH_2$), 31.3 ($CH_3$).

**Benzyloct-1-ynylcarbamic acid benzyl ester (395a)**




Following a slight modification of the procedure of Hsung and co-workers,[162a] a mixture of 1-bromooct-1-yne (3.17 g, 16.8 mmol), benzylcarbamic acid benzyl ester[183] (3.69 g, 15.3 mmol), $K_3PO_4$ (6.50 g, 30.6 mmol), $CuSO_4 \cdot 5H_2O$ (382 mg, 1.53 mmol), 1,10-phenanthroline (551 mg, 3.06 mmol) in toluene (30 mL) was heated at 80 °C for 40 h. After cooling to room temperature, the mixture was filtered through a short pad of silica gel using $CH_2Cl_2$ (100 mL) as the eluent, and the filtrate was concentrated *in vacuo*. Purification of the residue by column chromatography (10% EtOAc/hexane) gave the *ynamide* **395a** (2.07 g, 39%) as a yellow oil. $R_f$ = 0.28 (20% EtOAc/hexane); IR (film) 3054, 2986, 1719 (C=O), 1496, 1421, 1265, 1126, 896, 740, 705 $cm^{-1}$; $^1H$ NMR (360 MHz, $CDCl_3$) δ 7.38-7.31 (10H, m, Ar**H**), 5.23 (2H, s, OC**H**$_2$Ph), 4.62 (2H, s, NC**H**$_2$Ph), 2.25 (2H, t, *J* = 6.9 Hz, ≡C**H**$_2$), 1.49-1.41 (2H, m, ≡CH$_2$C**H**$_2$), 1.36-1.22 (6H, m, C**H**$_2$C**H**$_2$C**H**$_2$CH$_3$), 0.88 (3H, t, *J* = 6.9 Hz, C**H**$_3$); $^{13}C$ NMR (90.6 MHz, $CDCl_3$) δ 155.6 (C), 136.2 (C), 128.4 (4 x CH), 128.3 (CH), 128.1 (2 x CH), 127.9 (C), 127.8 (2 x CH), 127.7 (CH), 77.2 (C), 70.6 (C), 68.2 ($CH_2$), 53.8 ($CH_2$), 31.3 ($CH_2$), 28.8 ($CH_2$), 28.3 ($CH_2$), 22.5 ($CH_2$), 18.3 ($CH_2$), 14.0 ($CH_3$); HRMS (ES) Exact mass calcd for $C_{23}H_{31}N_2O_2$ $[M+NH_4]^+$: 367.2380, found: 367.2376.

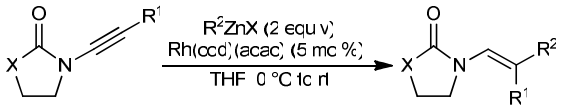
**Phenyl(phenylethynyl)carbamic acid *tert*-butyl ester**




Following the procedure of Hsung and co-workers,[162a] a mixture of 1-bromo-2-phenylacetylene (3.14 g, 17.3 mmol), *N*-Boc-aniline (3.04 g, 15.7 mmol), $K_3PO_4$ (6.67 g, 31.4 mmol), $CuSO_4 \cdot 5H_2O$ (392 mg, 1.57 mmol), and 1,10-phenanthroline (566 mg, 3.14 mmol) in toluene (30 mL) was heated at 65 °C for 44 h. After cooling to room temperature, the mixture was filtered through a short pad of silica gel using

$CH_2Cl_2$ (40 mL) as the eluent, and the filtrate was concentrated *in vacuo*. Purification of the residue by column chromatography (1% EtOAc/hexane) gave the *ynamide* **395b** (1.17 g, 25%) as a yellow solid that displayed identical spectroscopic data to those reported previously.[160] $R_f$ = 0.61 (20% EtOAc/hexane); mp = 62-64 °C; IR ($CHCl_3$) 2982 (C≡C), 1729 (C=O), 1597, 1493, 1369, 1294, 1154, 908, 733, 650 $cm^{-1}$; $^1H$ NMR (360 MHz, $CDCl_3$) δ 7.61-7.59 (1H, m, Ar**H**), 7.57-7.55 (1H, m, Ar**H**), 7.48-7.41 (5H, m, Ar**H**), 7.38-7.29 (4H, m, Ar**H**), 1.62 (9H, s, O($C\mathbf{H}_3$)$_3$); $^{13}C$ NMR (62.9 MHz, $CDCl_3$) δ 152.9 (C), 139.6 (C), 130.8 (2 x CH), 128.8 (2 x CH), 128.2 (2 x CH), 127.3 (CH), 126.6 (CH), 124.6 (CH), 123.3 (C), 83.6 (C), 83.5 (C), 70.1 (C), 28.0 (3 x $CH_3$).

### 6.2.2 Carbozincations Using Organozinc Halide Reagents




**General Procedure G**

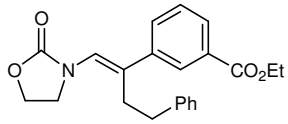
To a solution of the appropriate ynamide (1.0 equiv) and Rh(cod)(acac) (0.05 equiv) in THF (10 mL/mmol of ynamide) at 0 °C was added the appropriate organozinc halide (2 equiv) over 1 min, and the reaction was then stirred at room temperature until complete consumption of starting material was observed by TLC analysis.

**Workup D**

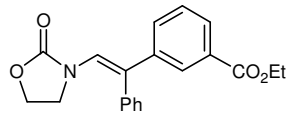
The reaction mixture was filtered through a short pad of silica gel using $CH_2Cl_2$ as eluent, and the filtrate was concentrated *in vacuo*.

**Workup E**

The reaction was quenched with saturated $NH_4Cl$ solution (10 mL) and the mixture was stirred vigorously for 15 min. The aqueous layer was separated and extracted with EtOAc (3 x 10 mL) and the combined organic layers were dried ($MgSO_4$), and concentrated *in vacuo*.

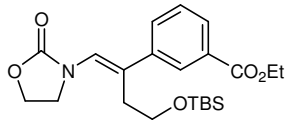


**3-{1-[1-(2-Oxooxazolidin-3-yl)-meth-(*E*)-ylidene]-3-phenylpropyl}benzoic acid ethyl ester (396a)**. The title compound was prepared according to General Procedure G using ynamide **394a** (43 mg, 0.20 mmol) and 3-(ethoxycarbonyl)phenylzinc iodide (0.5 M in THF, 0.80 mL, 0.40 mmol) for a reaction time of 1.5 h. Workup D and purification by column chromatography (30% EtOAc/hexane) gave the *enamide* **396a** as a yellow oil (55 mg, 75%). $R_f$ = 0.18 (30% EtOAc/hexane); IR (film) 2985, 1755 (C=O), 1714 (C=O), 1479, 1404, 1265, 1088, 1043, 908, 735 $cm^{-1}$; $^1H$ NMR (360 MHz, $CDCl_3$) δ 8.09 (1H, t, *J* = 1.6 Hz, Ar**H**), 7.99 (1H, dt, *J* = 7.8, 1.4 Hz, Ar**H**), 7.59 (1H, ddd, *J* = 7.8, 1.8, 1.2 Hz, Ar**H**), 7.45 (1H, t, *J* = 7.8 Hz, Ar**H**), 7.30-7.26 (2H, m, Ar**H**), 7.22-7.18 (1H, m, Ar**H**), 7.15-7.12 (2H, m, Ar**H**), 6.44 (1H, s, =C**H**), 4.42 (2H, q, *J* = 7.1 Hz, OC**H**$_2$CH$_3$), 4.33 (2H, app dd, *J* = 8.7, 7.2 Hz, OC**H**$_2$CH$_2$N), 3.66-3.58 (2H, m, C**H**$_2$N), 2.92 (2H, t, *J* = 7.6 Hz) and 2.68 (2H, t, *J* = 7.6 Hz, C**H**$_2$C**H**$_2$Ph), 1.43 (3H, t, *J* = 7.1 Hz, OCH$_2$C**H**$_3$); $^{13}C$ NMR (62.9 MHz, $CDCl_3$) δ 166.5 (C), 157.0 (C), 141.2 (C), 140.5 (C), 131.2 (CH), 130.8 (C), 130.0 (C), 128.6 (CH), 128.5 (3 x CH), 128.4 (2 x CH), 127.9 (CH), 126.2 (CH), 123.4 (CH), 62.3 ($CH_2$), 61.1 ($CH_2$), 45.9 ($CH_2$), 34.3 ($CH_2$), 31.5 ($CH_2$), 14.3 ($CH_3$); HRMS (ES) Exact mass calcd for $C_{22}H_{27}N_2O_4$ $[M+NH_4]^+$: 383.1965, found: 383.1966.

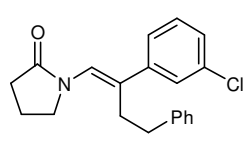


**3-[(*E*)-2-(2-Oxooxazolidin-3-yl)-1-phenylvinyl]benzoic acid ethyl ester (396b)**. The title compound was prepared according to General Procedure G from ynamide **394b** (94 mg, 0.50 mmol) and 3-(ethoxycarbonyl)phenylzinc iodide (0.5 M in THF, 2.00 mL, 1.00 mmol) for a reaction time of 5 h. Workup E and purification by column chromatography (15% EtOAc/hexane→30% EtOAc/hexane) gave the *enamide* **396b** as a pale yellow solid (98 mg, 58%). Slow diffusion of petrol into a solution of **396b** in $CH_2Cl_2$ gave colourless crystals that were suitable for X-ray crystallography. $R_f$ = 0.52 (50% EtOAc/hexane); m.p. 116-118 °C; IR ($CHCl_3$) 3055, 2986, 1758 (C=O), 1714 (C=O), 1614, 1402, 1413, 1266, 1216, 739, 705 $cm^{-1}$; $^1H$ NMR (360 MHz, $CDCl_3$) δ 7.94-7.87 (2H, m, Ar**H**), 7.44-7.22 (7H, m, Ar**H**), 7.19 (1H, s, =C**H**), 4.37

(2H, q, $J$ = 7.1 Hz, OC**H**$_2$CH$_3$), 4.27-4.16 (2H, m, OC**H**$_2$CH$_2$N), 3.22-3.10 (2H, m, C**H**$_2$N), 1.38 (3H, t, $J$ = 7.1 Hz, OCH$_2$C**H**$_3$); $^{13}$C NMR (90.6 MHz, $CDCl_3$) δ 166.5 (C), 157.2 (C), 141.3 (C), 137.5 (C), 131.6 (CH), 130.8 (2 x CH), 130.6 (C), 128.4 (2 x CH), 128.3 (CH), 128.1 (CH), 128.1 (CH), 127.9 (CH), 125.3 (C), 123.3 (CH), 62.7 ($CH_2$), 61.0 ($CH_2$), 44.8 ($CH_2$), 14.3 ($CH_3$); HRMS (ES) Exact mass calcd for $C_{20}H_{20}NO_4$ $[M+H]^+$: 338.1387, found: 338.1390.

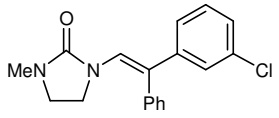



**3-{3-(*tert*-Butyldimethylsilyloxy)-1-[1-(2-oxooxazolidin-3-yl)meth-(*E*)-ylidene]propyl}benzoic acid ethyl ester (396c)**. The title compound was prepared according to General Procedure G using ynamide **394e** (54 mg, 0.20 mmol) and 3-(ethoxycarbonyl)phenylzinc iodide (0.5 M in THF, 0.80 mL, 0.40 mmol) for a reaction time of 2.5 h. Workup D and purification by column chromatography (30% EtOAc/hexane) gave the *enamide* **396c** as a brown oil (55 mg, 66%). $R_f$ = 0.55 (50% EtOAc/hexane); IR (film) 2956, 1755 (C=O), 1714 (C=O), 1651, 1471, 1254, 1099, 908, 735, 650 cm$^{-1}$; $^1$H NMR (360 MHz, $CDCl_3$) δ 8.00 (1H, dd, $J$ = 2.3, 1.2 Hz, Ar**H**), 7.95 (1H, dt, $J$ = 7.8, 1.2 Hz, Ar**H**), 7.53 (1H, ddd, $J$ = 7.8, 2.3, 1.2 Hz, Ar**H**), 7.40 (1H, t, $J$ = 7.8 Hz, Ar**H**), 6.65 (1H, s, =C**H**), 4.47-4.43 (2H, m, OC**H**$_2$CH$_2$N), 4.39 (2H, q, $J$ = 7.1 Hz, OC**H**$_2$CH$_3$), 4.15 (2H, app dd, $J$ = 9.0, 7.0 Hz, C**H**$_2$N), 3.60 (2H, t, $J$ = 6.4 Hz, C**H**$_2$OSi), 2.86 (2H, t, $J$ = 6.4 Hz, C**H**$_2$CH$_2$OSi), 1.41 (3H, t, $J$ = 7.1 Hz, OCH$_2$C**H**$_3$), 0.84 (9H, s, C(C**H**$_3$)$_3$), –0.05 (6H, s, Si(C**H**$_3$)$_2$); $^{13}$C NMR (62.9 MHz, $CDCl_3$) δ 166.5 (C), 157.3 (C), 141.0 (C), 131.4 (CH), 130.6 (C), 128.4 (CH), 128.3 (CH), 127.9 (CH), 125.0 (C), 124.6 (CH), 62.5 ($CH_2$), 61.0 ($CH_2$), 60.9 ($CH_2$), 46.2 ($CH_2$), 32.7 ($CH_2$), 25.8 (3 x $CH_3$), 18.2 (C), 14.3 ($CH_3$), –5.5 (2 x $CH_3$); HRMS (ES) Exact mass calcd for $C_{22}H_{37}N_2O_5Si$ $[M+NH_4]^+$: 437.2466, found: 437.2469.

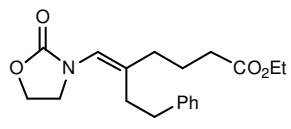



**1-[(*E*)-2-(3-Chlorophenyl)-4-phenylbut-1-enyl]pyrrolidin-2-one (396d)**. The title compound was prepared according to General Procedure G from ynamide **394g** (43 mg, 0.20 mmol) and 3-chlorophenylzinc iodide (0.5 M in THF, 0.80 mL, 0.40 mmol) for a reaction time of 5 h. Workup E and purification by column chromatography (40%

EtOAc/hexane) gave the *enamide* **396d** as a brown oil (50 mg, 77%). $R_f$ = 0.40 (60% EtOAc/hexane); IR (film) 3054, 1699 (C=O), 1641, 1591, 1460, 1415, 1265, 1226, 736, 701 $cm^{-1}$; $^1H$ NMR (360 MHz, $CDCl_3$) δ 7.39 (1H, dt, *J* = 2.6, 1.2 Hz, Ar**H**), 7.32-7.24 (5H, m, Ar**H**), 7.23-7.17 (1H, m, Ar**H**), 7.15-7.13 (2H, m, Ar**H**), 6.55 (1H, s, =C**H**), 3.55-3.50 (2H, m, C**H**$_2$N), 2.86 (2H, app dd, *J* = 9.1, 6.5 Hz) and 2.68 (2H, app dd, *J* = 9.1, 6.5 Hz, C**H**$_2$C**H**$_2$Ph), 2.43 (2H, t, *J* = 8.1 Hz, C**H**$_2$C=O), 2.09-2.01 (2H, m, C**H**$_2$CH$_2$N); $^{13}C$ NMR (90.6 MHz, $CDCl_3$) δ 174.9 (C), 142.8 (C), 141.3 (C), 134.3 (C), 129.6 (CH), 129.1 (C), 128.4 (4 x CH), 127.2 (CH), 127.0 (CH), 126.1 (CH), 125.0 (CH), 123.8 (CH), 48.9 ($CH_2$), 34.5 ($CH_2$), 31.9 ($CH_2$), 30.4 ($CH_2$), 18.8 ($CH_2$); HRMS (ES) Exact mass calcd for $C_{20}H_{20}ClNONa$ $[M+Na]^+$: 348.1126, found: 348.1125.

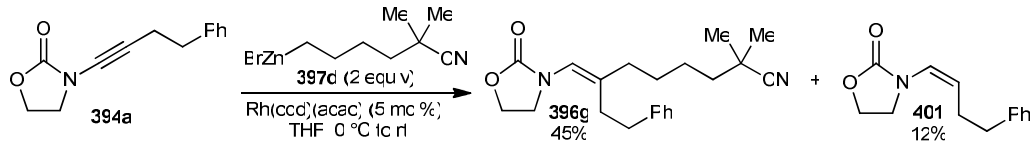



**1-[(*E*)-2-(3-Chlorophenyl)-2-phenylvinyl]-3-methylimidazolidin-2-one (396e)**. The title compound was prepared according to General Procedure G from ynamide **394i** (40 mg, 0.20 mmol) and 3-chlorophenylzinc iodide (0.5 M in THF, 0.80 mL, 0.40 mmol) for a reaction time of 5 h. Workup E and purification by column chromatography (40% EtOAc/hexane) gave the *enamide* **396e** as a yellow oil (51 mg, 82%). $R_f$ = 0.40 (60% EtOAc/hexane); IR (film) 3054, 1711 (C=O), 1634, 1589, 1483, 1435, 1362, 1265, 896, 737 $cm^{-1}$; $^1H$ NMR (360 MHz, $CDCl_3$) δ 7.40-7.28 (4H, m, Ar**H**), 7.26-7.21 (2H, m, Ar**H**), 7.18-7.09 (3H, m, Ar**H** and =C**H**), 7.05 (1H, ddd, *J* = 6.7, 2.8, 1.2 Hz, Ar**H**), 3.24-3.17 (2H, m, C**H**$_2$N), 3.01-2.93 (2H, m, C**H**$_2$N), 2.86 (3H, s, C**H**$_3$); $^{13}C$ NMR (90.6 MHz, $CDCl_3$) δ 158.4 (C), 144.1 (C), 138.4 (C), 134.0 (C), 131.2 (2 x CH), 129.2 (CH), 128.1 (2 x CH), 127.4 (CH), 126.7 (CH), 125.9 (CH), 125.1 (CH), 124.8 (CH), 119.4 (C), 44.8 ($CH_2$), 42.6 ($CH_2$), 31.0 ($CH_3$); HRMS (ES) Exact mass calcd for $C_{18}H_{17}ClN_2ONa$ $[M+Na]^+$: 335.0922, found: 335.0922.




**5-[1-(2-Oxooxazolidin-3-yl)meth-(*Z*)-ylidene]-7-phenylheptanoic acid ethyl ester (396f)**. The *enamide* **396f** was prepared by Benoit Gourdet as described previously.[160]

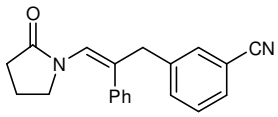
**2,2-Dimethyl-7-[1-(2-oxooxazolidin-3-yl)meth-(*Z*)-ylidene]-9-phenylnonanenitrile (396g)**




General Procedure G was followed using ynamide **394a** (43 mg, 0.20 mmol) and 5-cyano-5-methylhexylzinc bromide (0.5 M in THF, 0.80 mL, 0.40 mmol) for a reaction time of 4 h. Workup E and purification by column chromatography (30% EtOAc/hexane→40% EtOAc/hexane) gave the *enamide* **401** (5 mg, 12%) as a brown oil followed by the *enamide* **396g** (30 mg, 45%) as a yellow oil.

Data for **401**: See page 173.

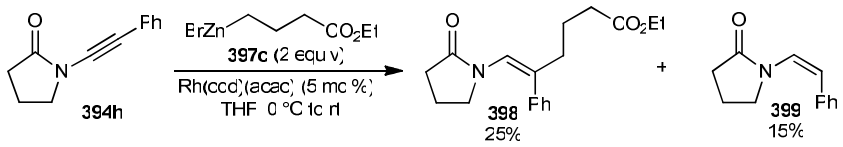
Data for **396g**: $R_f$ = 0.44 (50% EtOAc/hexane); IR (film) 3055, 2305 (C≡N), 1753 (C=O), 1670, 1603, 1410, 1265, 1088, 895, 739 $cm^{-1}$; $^1H$ NMR (360 MHz, $CDCl_3$) δ 7.33-7.25 (2H, m, Ar**H**), 7.23-7.16 (3H, m, Ar**H**), 5.87 (1H, s, =C**H**), 4.30-4.22 (2H, m, C**H**$_2$O), 3.51-3.45 (2H, m, C**H**$_2$N), 2.74 (2H, app dd, *J* = 8.8, 6.9 Hz) and 2.41 (2H, app dd, *J* = 8.8, 6.9 Hz, C**H**$_2$C**H**$_2$Ph), 2.15 (2H, t, *J* = 6.1 Hz, C**H**$_2$(CH$_2$)$_3$C(CH$_3$)$_2$), 1.67-1.49 (6H, m, (C**H**$_2$)$_3$C(CH$_3$)$_2$CN), 1.35 (6H, s, C(C**H**$_3$)$_2$CN); $^{13}C$ NMR (62.9 MHz, $CDCl_3$) δ 157.1 (C), 141.5 (C), 134.1 (C), 131.4 (C), 128.4 (2 x CH), 128.4 (2 x CH), 126.1 (CH), 119.8 (CH), 62.1 ($CH_2$), 46.3 ($CH_2$), 40.8 ($CH_2$), 34.0 ($CH_2$), 33.9 ($CH_2$), 32.4 (C), 31.4 ($CH_2$), 27.9 ($CH_2$), 26.6 (2 x $CH_3$), 24.9 ($CH_2$); HRMS (ES) Exact mass calcd for $C_{21}H_{32}N_3O_2$ $[M+NH_4]^+$: 358.2489, found: 358.2486.




**3-[(*Z*)-3-(2-Oxopyrrolidin-1-yl)-2-phenylallyl]benzonitrile (396h)**. The title compound was prepared according to a slight modification of General Procedure G, in which $[Rh(cod)Cl]_2$ (4.9 mg, 0.01mmol) and *rac*-BINAP (12.5 mg, 0.02 mmol) were used in place of Rh(cod)(acac), using ynamide **394h** (37 mg, 0.20 mmol) and 3-cyanobenzylzinc bromide (0.5 M in THF, 0.80 mL, 0.40 mmol) at 60 °C for a reaction time of 6 h. Workup E and purification by column chromatography (20%

EtOAc/hexane→50%EtOAc/hexane) gave the *enamide* **396h** as a pale orange solid (20 mg, 35%). $R_f$ = 0.36 (60% EtOAc/hexane); m.p. 86-88 °C; IR ($CHCl_3$) 2923, 2228 (C≡N), 1695 (C=O), 1483, 1398, 1299, 1266, 789, 727, 704 $cm^{-1}$; $^1H$ NMR (360 MHz, $CDCl_3$) δ 7.40-7.34 (1H, m, Ar**H**), 7.37-7.29 (3H, m, Ar**H**), 7.24-7.21 (3H, m, Ar**H**), 6.99-6.93 (3H, m, Ar**H** and =C**H**), 3.67 (2H, s, C**H**$_2$Ar), 2.93-2.86 (2H, m, C**H**$_2$N), 2.37 (2H, t, *J* = 8.1 Hz, C**H**$_2$C=O), 1.87-1.78 (2H, m, C**H**$_2$CH$_2$N); $^{13}C$ NMR (90.6 MHz, $CDCl_3$) δ 175.2 (C), 140.8 (C), 138.3 (C), 133.5 (CH), 132.4 (CH), 130.1 (CH), 129.1 (2 x CH), 129.0 (CH), 127.9 (2 x CH), 127.5 (CH), 123.9 (C), 122.6 (CH), 118.9 (C), 112.1 (C), 48.1 ($CH_2$), 44.1 ($CH_2$), 30.3 ($CH_2$), 18.6 ($CH_2$); HRMS (ES) Exact mass calcd for $C_{20}H_{19}N_2O$ $[M+H]^+$: 303.1492, found: 303.1489.

**(*Z*)-6-(2-Oxopyrrolidin-1-yl)-5-phenylhex-5-enoic acid ethyl ester (398) and 1-[(*Z*)-styryl]pyrrolidin-2-one (399)[184]**



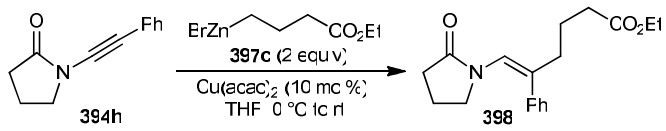

General Procedure G was followed using ynamide **394h** (37 mg, 0.20 mmol) and 4-ethoxy-4-oxobutylzinc bromide (0.5 M in THF, 0.80 mL, 0.40 mmol) for a reaction time of 6 h. Workup E and purification by column chromatography (30% EtOAc/hexane→50% EtOAc/hexane) to gave *enamide* **399** (5 mg, 15%) as a yellow oil followed by the *enamide* **398** (14 mg, 25%) as a yellow oil.

Data for **398**: $R_f$ = 0.31 (50% EtOAc/hexane); IR (film) 2983, 1724 (C=O), 1682 (C=O), 1404, 1321, 1265, 1095, 1026, 912, 744, 650 $cm^{-1}$; $^1H$ NMR (360 MHz, $CDCl_3$) δ 7.36-7.24 (3H, m, Ar**H**), 7.19-7.15 (2H, m, Ar**H**), 6.75 (1H, s, =C**H**), 4.10 (2H, q, *J* = 7.1 Hz, OC**H**$_2$CH$_3$), 2.92-2.85 (2H, m, C**H**$_2$N), 2.43-2.26 (6H, m, C**H**$_2$CH$_2$CH$_2$N and C**H**$_2$CH$_2$C**H**$_2$CO$_2$Et), 1.84-1.76 (2H, m) and 1.71-1.59 (2H, m, C**H**$_2$CH$_2$N and C**H**$_2$CH$_2$CO$_2$Et), 1.24 (3H, t, *J* = 7.1 Hz, OCH$_2$C**H**$_3$); $^{13}C$ NMR (90.6 MHz, $CDCl_3$) δ 175.0 (C), 173.4 (C), 139.2 (C), 129.0 (2 x CH), 128.0 (2 x CH), 127.2 (CH), 126.0 (C), 121.1 (CH), 60.2 ($CH_2$), 48.2 ($CH_2$), 37.3 ($CH_2$), 33.6

($CH_2$), 30.4 ($CH_2$), 23.5 ($CH_2$), 18.7 ($CH_2$), 14.2 ($CH_3$); HRMS (ES) Exact mass calcd for $C_{18}H_{24}NO_3$ $[M+H]^+$: 302.1751, found: 302.1749.

Data for **399**: $R_f$ = 0.47 (50% EtOAc/hexane); IR (film) 2925, 1691 (C=O), 1462, 1412, 1383, 1265, 1095, 908, 737, 650 $cm^{-1}$; $^1H$ NMR (360 MHz, $CDCl_3$) δ 7.42-7.11 (5H, m, Ar**H**), 6.81 (1H, d, *J* = 9.9 Hz, C**H**=CHPh), 6.01 (1H, d, *J* = 9.9 Hz, CH=C**H**Ph), 3.25-3.16 (2H, m, C**H**$_2$N), 2.45-2.38 (2H, m, C**H**$_2$C=O), 1.99-1.91 (2H, m, C**H**$_2$$CH_2$N); $^{13}C$ NMR (90.7 MHz, $CDCl_3$) δ 175.6 (C), 136.3 (C), 129.2 (2 x CH), 127.8 (2 x CH), 126.9 (CH), 123.9 (CH), 113.8 (CH), 48.0 ($CH_2$), 30.3 ($CH_2$), 18.8 ($CH_2$). Spectroscopic data were consistent with those observed previously.[184]

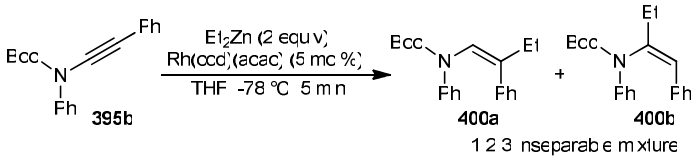
Using alternative copper-catalysed conditions:




To a solution of the ynamide **394h** (93 mg, 0.50 mmol) and $Cu(acac)_2$ (13.1 mg, 0.05 mmol) in THF (5 mL) at 0 °C was added 4-ethoxy-4-oxobutylzinc bromide (0.5 M in THF, 2.0 mL, 1.0 mmol). The reaction was stirred at room temperature for 5 h, quenched with saturated $NH_4Cl$ solution (10 mL), and the mixture stirred vigorously for 30 min. The aqueous layer was separated and extracted with $CH_2Cl_2$ (3 x 20 mL) and the combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. Purification of the residue by column chromatography (30% EtOAc/hexane→50% EtOAc/hexane) gave the *enamide* **398** as a yellow oil (112 mg, 74%).

### 6.2.3 Carbozincation of Acyclic Ynamides

***N*-Phenyl-*N*-[(*Z*)-2-phenylbut-1-enyl]carbamic acid *tert*-butyl ester (400a) and *N*-phenyl-*N*-{1-[1-phenylmeth-(*Z*)-ylidene]propyl}carbamic acid *tert*-butyl ester (400b)**[*]




To a solution of ynamide **395b** (88 mg, 0.30 mmol) and Rh(cod)(acac) 4.6 mg, 0.015 mmol) in THF (3 mL) at –78 °C was added $Et_2Zn$ (0.5 M in THF, 1.20 mL, 0.60 mmol) dropwise over 2 min, and the reaction was then stirred at –78 °C for 5 min. The mixture was quenched with saturated aqueous $NH_4Cl$ solution (10 mL) and extracted with $CH_2Cl_2$ (3 x 10 mL). The organic layers were combined, dried ($MgSO_4$), and concentrated *in vacuo*. Purification of the residue by column chromatography (1/20 EtOAc/hexane) afforded a 1:2.3 inseparable mixture of *enamides* **400a** and **400b** (77 mg, 80%) as a pale orange oil. $R_f$ = 0.60 (20% EtOAc/hexane); IR (film) 2974, 2934, 2360 (C=C), 1709 (C=O), 1493, 1367, 1302, 1161, 1018, 754 $cm^{-1}$.

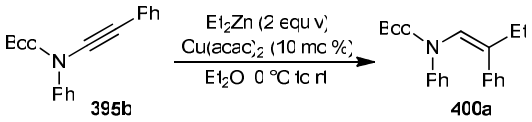
NMR data for minor isomer **400a**: $^1H$ NMR (360 MHz, $CDCl_3$) δ 7.57-6.98 (10H, m, Ar**H**), 6.51 (1H, br s, =C**H**), 2.46 (2H, dq, *J* = 7.4, 1.3 Hz, C**H**$_2$CH$_3$), 1.42 (9H, s, C(C**H**$_3$)$_3$), 1.08 (3H, t, *J* = 7.4 Hz, CH$_2$C**H**$_3$); $^{13}C$ NMR (62.9 MHz, $CDCl_3$) δ 153.6 (C), 142.0 (C), 138.9 (C), 127.8 (4 x CH and C), 126.6 (2 x CH), 125.8 (2 x CH), 124.6 (2 x CH), 124.3 (CH), 80.8 (C), 29.3 ($CH_2$), 28.1 (3 x $CH_3$), 13.2 ($CH_3$).

NMR data for major isomer **400b**: $^1H$ NMR (360 MHz, $CDCl_3$) δ 7.57-6.98 (10H, m, Ar**H**), 6.41 (1H, s, =C**H**), 2.26 (2H, q, *J* = 7.4 Hz, C**H**$_2$CH$_3$), 1.24 (9H, s, C(C**H**$_3$)$_3$), 1.15 (3H, t, *J* = 7.4 Hz, CH$_2$C**H**$_3$); $^{13}C$ NMR (62.9 MHz, $CDCl_3$) δ 152.7 (C), 140.4 (C), 140.0 (C), 136.0 (C), 128.7 (2 x CH), 128.6 (2 x CH), 127.4 (2 x CH), 127.2 (CH), 125.1 (CH), 124.7 (CH), 124.1 (2 x CH), 80.5 (C), 28.6 ($CH_2$), 27.7 (3 x $CH_3$), 11.7 ($CH_3$).

[*] This experiment was carried out by Benoit Gourdet.

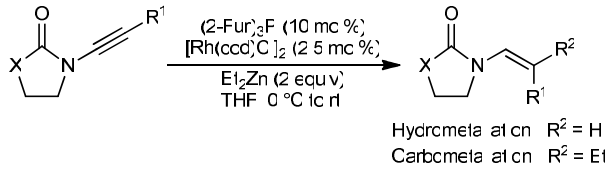
HRMS (ES) Exact mass calcd for $C_{21}H_{26}NO_2$ $[M+H]^+$: 324.1958, found: 324.1956.

**_N_-Phenyl-_N_-[(_Z_)-2-phenylbut-1-enyl]carbamic acid _tert_-butyl ester (400a)**




To a solution of ynamide **395b** (147 mg, 0.50 mmol) and $Cu(acac)_2$ (13.1 mg, 0.05 mmol) in $Et_2O$ (5 mL) at 0 °C was added $Et_2Zn$ (1.0 M in hexane, 1.00 mL, 1.00 mmol) over 1 min and the mixture was then stirred at room temperature for 16 h. The reaction was quenched with saturated aqueous $NH_4Cl$ solution (10 mL) and extracted with $CH_2Cl_2$ (3 x 10 mL). The combined organic layers were dried ($MgSO_4$), and concentrated *in vacuo*. Purification of the residue by column chromatography (1% EtOAc/hexane) gave the *enamide* **400a** (106 mg, 66%) as a pale orange oil. $R_f$ = 0.60 (20% EtOAc/hexane); IR (film) 2975, 1700 (C=O), 1597, 1493, 1340, 1266, 1160, 1018, 864, 741 $cm^{-1}$; $^1H$ NMR (360 MHz, $CDCl_3$) δ 7.16-7.04 (5H, m, Ar**H**), 7.03-6.92 (5H, m, Ar**H**), 6.46 (1H, br s, =C**H**), 2.41 (2H, dq, *J* = 7.4, 1.3 Hz, C**H**$_2$CH$_3$), 1.37 (9H, s, C(C**H**$_3$)$_3$), 1.03 (3H, t, *J* = 7.4 Hz, CH$_2$C**H**$_3$); $^{13}C$ NMR (62.9 MHz, $CDCl_3$) δ 153.6 (C), 142.0 (C), 138.9 (C), 127.8 (4 x CH and C), 126.6 (2 x CH), 125.8 (2 x CH), 124.6 (2 x CH), 124.3 (CH), 80.8 (C), 29.3 ($CH_2$), 28.1 (3 x $CH_3$), 13.2 ($CH_3$); HRMS (ES) Exact mass calcd for $C_{21}H_{26}NO_2$ $[M+H]^+$: 324.1958, found: 324.1956.

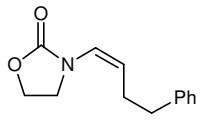
## 6.2.4 Hydrometallation of Ynamides



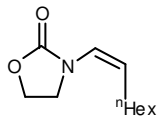

**General Procedure H**

To a stirred solution of the appropriate ynamide (1.0 equiv), $[Rh(cod)Cl]_2$ (0.025 equiv) and tri(2-furyl)phosphine (0.10 equiv) in THF (10 mL/mmol of ynamide) at 0

°C was added $Et_2Zn$ (1.0 M in hexane, 2.0 equiv) over 1 min and the reaction was then stirred at room temperature until complete consumption of starting material was observed by TLC analysis (up to 6 h). The mixture was filtered through a short pad of silica gel using $CH_2Cl_2$ (30 mL) as eluent, and the filtrate was concentrated *in vacuo*. Purification of the residue by column chromatography afforded the desired enamide.

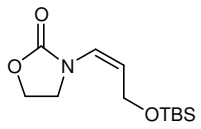


**3-[(*Z*)-4-Phenylbut-1-enyl]oxazolidin-2-one (401)**. The title compound was prepared according to General Procedure H from ynamide **394a** (43 mg, 0.20 mmol) for a reaction time of 1.5 h. Purification by column chromatography (40% EtOAc/hexane) gave a 9:1 mixture of the *enamide* **401** and the carbometallation product **392b** (26 mg, 60%) as a brown oil. $R_f$ = 0.55 (50% EtOAc/hexane); IR (film) 2930, 1753 (C=O), 1668, 1481, 1419, 1246, 1078, 908, 737, 650 $cm^{-1}$; $^1H$ NMR (360 MHz, $CDCl_3$) δ 7.32-7.28 (2H, m, Ar**H**), 7.24-7.18 (3H, m, Ar**H**), 6.26 (1H, dt, *J* = 9.5, 1.6 Hz, C**H**=CHCH$_2$), 4.89 (1H, dt, *J* = 9.5, 7.6 Hz, CH=C**H**CH$_2$), 4.34-4.29 (2H, m, C**H**$_2$O), 3.78-3.74 (2H, m, C**H**$_2$N), 2.73 (2H, t, *J* = 7.6 Hz, C**H**$_2$Ph), 2.50 (2H, app qd, *J* = 7.4, 1.5 Hz, C**H**$_2$CH$_2$Ph); $^{13}C$ NMR (62.9 MHz, $CDCl_3$) δ 156.8 (C), 141.2 (C), 128.5 (2 x CH), 128.4 (2 x CH), 126.1 (CH), 122.9 (CH), 114.5 (CH), 62.1 ($CH_2$), 45.4 ($CH_2$), 36.2 ($CH_2$), 28.6 ($CH_2$); HRMS (ES) Exact mass calcd for $C_{13}H_{16}NO_2$ $[M+H]^+$: 218.1176, found: 218.1179.

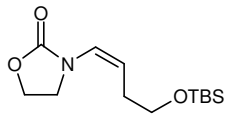


**(*Z*)-3-Oct-1-enyl]oxazolidin-2-one (402a)**. The title compound was prepared according to General Procedure H from ynamide **394c** (39 mg, 0.20 mmol) for a reaction time of 30 min. Purification by column chromatography (20% EtOAc/hexane) gave an 11:1 mixture of the *enamide* **402a** and the corresponding carbometallation product (18 mg, 46%) as a yellow oil. $R_f$ = 0.58 (40% EtOAc/hexane); IR (film) 2927, 1753 (C=O), 1668, 1481, 1419, 1265, 1078, 908, 737, 650, 447 $cm^{-1}$; $^1H$ NMR (360 MHz, $CDCl_3$) δ 6.23 (1H, dt, *J* = 9.4, 1.6 Hz, C**H**=CHCH$_2$), 4.84 (1H, dt, *J* = 9.4, 7.6 Hz, CH=C**H**CH$_2$), 4.43-4.35 (2H, m, C**H**$_2$O), 3.96 (2H, app dd, *J* = 8.9, 7.1 Hz, C**H**$_2$N), 2.16 (2H, app qd, *J* = 7.6, 1.6 Hz, =CC**H**$_2$), 1.42-1.28 (8H, m, (C**H**$_2$)$_4$CH$_3$), 0.91-0.86 (3H, m, (CH$_2$)$_4$C**H**$_3$); $^{13}C$ NMR

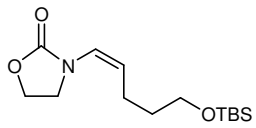
(62.9 MHz, $CDCl_3$) δ 156.9 (C), 122.3 (CH), 116.0 (CH), 62.1 ($CH_2$), 45.7 ($CH_2$), 31.6 ($CH_2$), 30.1 ($CH_2$), 28.9 ($CH_2$), 26.5 ($CH_2$), 22.6 ($CH_2$), 14.0 ($CH_3$); HRMS (ES) Exact mass calcd for $C_{11}H_{20}NO_2$ $[M+H]^+$: 198.1489, found: 198.1487.



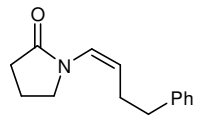

**3-[(*Z*)-3-(*tert*-Butyldimethylsilyloxy)propenyl]oxazolidin-2-one (402b)**. The title compound was prepared according to General Procedure H from ynamide **394d** (128 mg, 0.50 mmol) for a reaction time of 4.5 h. Purification by column chromatography (15% EtOAc/hexane) gave a 9:1 mixture of the *enamide* **402b** and the corresponding carbometallation product (74 mg, 58%) as a yellow oil. $R_f$ = 0.17 (20% EtOAc/hexane); IR (film) 2929, 2858, 1756 (C=O), 1665, 1398, 1251, 1081, 909, 838, 733 $cm^{-1}$; $^1H$ NMR (360 MHz, $CDCl_3$) δ 6.31 (1H, dt, *J* = 9.7, 1.2 Hz, C**H**=CHCH$_2$), 5.00 (1H, dt, *J* = 9.7, 7.0 Hz, CH=C**H**CH$_2$), 4.40-4.35 (2H, m, C**H**$_2$O), 4.24 (2H, dd, *J* = 7.0, 1.2 Hz, C**H**$_2$OSi), 4.00 (2H, app dd, *J* = 8.9, 7.1 Hz, C**H**$_2$N), 0.87 (9H, s, C(C**H**$_3$)$_3$), 0.05 (6H, s, Si(C**H**$_3$)$_2$); $^{13}C$ NMR (62.9 MHz, $CDCl_3$) δ 156.5 (C), 123.8 (CH), 113.0 (CH), 62.1 ($CH_2$), 57.7 ($CH_2$), 45.1 ($CH_2$), 25.8 (3 x $CH_3$), 18.1 (C), –5.1 (2 x $CH_3$); *m/z*: No mass ion peaks observed under a range of mass spectroscopic techniques.




**3-[(*Z*)-4-(*tert*-Butydimethylsilyloxy)but-1-enyl]oxazolidin-2-one (402c)**. The title compound was prepared according to General Procedure H from ynamide **394e** (133 mg, 0.50 mmol) for a reaction time of 2 h. Purification by column chromatography (15% EtOAc/hexane) gave the *enamide* **402c** as a yellow oil (79 mg, 58%). $R_f$ = 0.40 (30% EtOAc/hexane); IR (film) 2956, 2929, 2858, 1753 (C=O), 1671, 1251, 1099, 909, 736 $cm^{-1}$; $^1H$ NMR (360 MHz, $CDCl_3$) δ 6.35 (1H, dt, *J* = 9.7, 1.5 Hz, C**H**=CHCH$_2$), 4.81 (1H, dt, *J* = 9.7, 7.8 Hz, CH=C**H**CH$_2$), 4.38 (2H, app dd, *J* = 9.0, 7.0 Hz, C**H**$_2$O), 4.02 (2H, app dd, *J* = 9.0, 7.0 Hz, C**H**$_2$N), 3.64 (2H, t, *J* = 6.5 Hz, C**H**$_2$OSi), 2.39 (2H, dtd, *J* = 7.8, 6.5, 1.5 Hz, C**H**$_2$CH$_2$OSi), 0.89 (9H, s, C(C**H**$_3$)$_3$), 0.05 (6H, s, Si(C**H**$_3$)$_2$); $^{13}C$ NMR (62.9 MHz, $CDCl_3$) δ 156.8 (C), 123.8 (CH), 110.7 (CH), 62.6 ($CH_2$), 62.2 ($CH_2$), 45.5 ($CH_2$), 30.1 ($CH_2$), 25.9 (3 x $CH_3$), 18.3 (C), –5.4 (2 x $CH_3$); HRMS (ES) Exact mass calcd for $C_{13}H_{26}NO_3Si$ $[M+H]^+$: 272.1676, found: 272.1677.



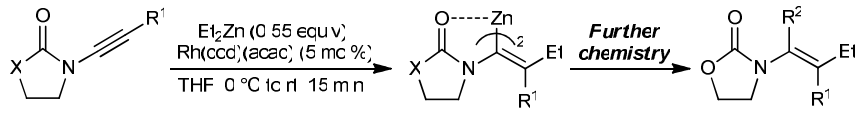
**3-[(*Z*)-5-(*tert*-Butyldimethylsilyloxy)pent-1-enyl]oxazolidin-2-one (402d)**. The title compound was prepared according to General Procedure H from ynamide **394f** (142 mg, 0.50 mmol) for a reaction time of 4.5 h. Purification by column chromatography (15% EtOAc/hexane) gave a 6:1 mixture of the *enamide* **402d** and the corresponding carbometallation product (59 mg, 42%) as a brown oil. $R_f$ = 0.18 (20% EtOAc/hexane); IR (film) 2959, 2930, 1751 (C=O), 1419, 1251, 1099, 908, 836, 735, 650 $cm^{-1}$; $^1H$ NMR (360 MHz, $CDCl_3$) δ 6.27 (1H, dt, *J* = 9.5, 1.4 Hz, C**H**=CHCH$_2$), 4.81 (1H, dt, *J* = 9.5, 7.8 Hz, CH=C**H**CH$_2$), 4.42-4.31 (2H, m, OC**H**$_2$CH$_2$N), 4.00 (2H, app dd, *J* = 9.0, 7.0 Hz, C**H**$_2$N), 3.62 (2H, t, *J* = 6.0 Hz, C**H**$_2$OSi), 2.25 (2H, app qd, *J* = 7.8, 1.4 Hz, =CHC**H**$_2$), 1.64-1.56 (2H, m, C**H**$_2$CH$_2$OSi), 0.88 (9H, s, C(C**H**$_3$)$_3$), 0.04 (6H, s, Si(C**H**$_3$)$_2$; $^{13}C$ NMR (62.9 MHz, $CDCl_3$) δ 156.9 (C), 122.8 (CH), 114.5 (CH), 62.1 ($CH_2$), 61.9 ($CH_2$), 45.5 ($CH_2$), 33.1 ($CH_2$), 25.8 (3 x $CH_3$), 22.7 ($CH_2$), 18.2 (C), –5.4 (2 x $CH_3$); HRMS (ES) Exact mass calcd for $C_{14}H_{28}NO_3Si$ $[M+H]^+$: 286.1833, found: 286.1829.



**1-[(*Z*)-4-Phenylbut-1-enyl]pyrrolidin-2-one (402f)**. The title compound was prepared according to General Procedure H from ynamide **394g** (64 mg, 0.30 mmol) for a reaction time of 30 min. Purification by column chromatography (50% EtOAc/hexane) gave the *enamide* **402f** as a yellow oil (34 mg, 53%). $R_f$ = 0.37 (50% EtOAc/hexane); IR (film) 2985, 1687 (C=O), 1460, 1417, 1387, 1265, 1095, 908, 739, 650 $cm^{-1}$; $^1H$ NMR (360 MHz, $CDCl_3$) δ 7.31-7.2 (2H, m, Ar**H**), 7.22-7.18 (3H, m, Ar**H**), 6.39 (1H, dt, *J* = 9.6, 1.4 Hz, C**H**=CHCH$_2$), 4.90 (1H, dt, *J* = 9.6, 7.6 Hz, CH=C**H**CH$_2$), 3.62 (2H, t, *J* = 7.5 Hz, C**H**$_2$N), 2.72 (2H, t, *J* = 7.6 Hz, CH$_2$C**H**$_2$Ph), 2.52 (2H, app qd, *J* = 7.6, 1.4 Hz, C**H**$_2$CH$_2$Ph), 2.39 (2H, t, *J* = 7.5 Hz, C**H**$_2$C=O), 2.03 (2H, app quintet, *J* = 7.5 Hz, CH$_2$C**H**$_2$CH$_2$N); $^{13}C$ NMR (62.9 MHz, $CDCl_3$) δ 174.5 (C), 141.4 (C), 128.4 (2 x CH), 128.3 (2 x CH), 126.0 (CH), 122.7 (CH), 115.5 (CH), 48.4 ($CH_2$), 36.3 ($CH_2$), 30.2 ($CH_2$), 29.2 ($CH_2$), 18.5 ($CH_2$); HRMS (ES) Exact mass calcd for $C_{14}H_{18}NO$ $[M+H]^+$: 216.1383, found: 216.1385.

### 6.2.5 Functionalisation of Alkenylzinc Intermediates

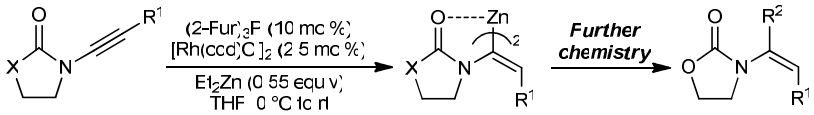
**Synthesis of Trisubstituted Enamides**




**General Procedure I**

To a solution of the appropriate ynamide (1.0 equiv) and Rh(cod)(acac) (0.05 equiv) in THF (10 mL/mmol of ynamide) at 0 °C was added $Et_2Zn$ (1.0 M in hexane, 0.55 equiv) over 0.5 min, and the reaction was then stirred at room temperature for 15 min to produce the alkenylzinc species. After addition of the appropriate electrophile and other catalysts/reagents and completion of the reaction, the mixture was quenched with saturated $NH_4Cl$ solution (10 mL) and extracted with $CH_2Cl_2$ (3 x 10 mL). The combined organic layers were dried ($MgSO_4$), and concentrated *in vacuo*. Purification of the residue by column chromatography afforded the desired enamide.

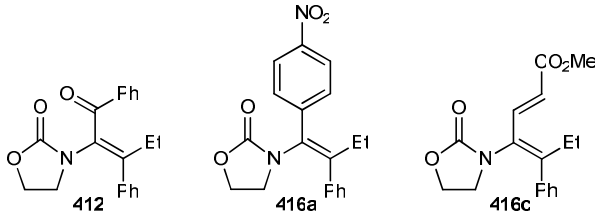
**Synthesis of α,β-Disubstituted Enamides**



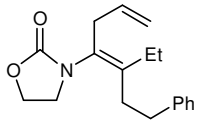

**General Procedure J**

To a solution of the appropriate ynamide (1.0 equiv), $[Rh(cod)Cl]_2$ (0.025 equiv) and tri(2-furyl)phosphine (0.10 equiv) in THF (10 mL/mmol of ynamide) at 0 °C was added $Et_2Zn$ (1.0 M in hexane, 0.55 equiv) and the reaction was then stirred at room temperature until complete consumption of starting material was observed by TLC analysis (2-6 h). After addition of the appropriate electrophile and other catalysts/reagents and completion of the reaction, the mixture was filtered through a short pad of silica gel using $CH_2Cl_2$ (30 mL) as eluent, and the filtrate was

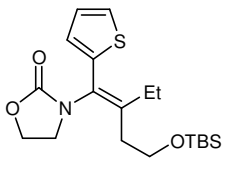
concentrated *in vacuo*. Purification of the residue by column chromatography afforded the desired enamide.




Benoit Gourdet prepared enamides **412**, **416a** and **416c** as described previously.[160]



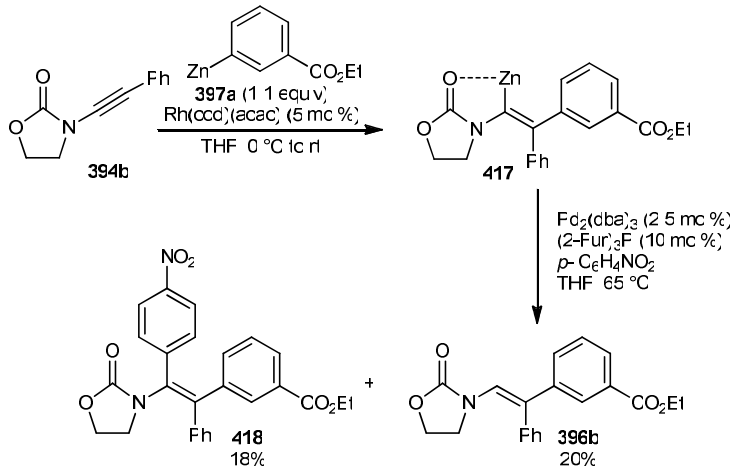

**3-[(*Z*)-1-Allyl-2-ethyl-4-phenylbut-1-enyl]oxazolidin-2-one (414)**. General Procedure I was followed using ynamide **394a** (109 mg, 0.50 mmol) to produce alkenylzinc species **413**. To this solution was added a solution of allyl bromide (217 μL, 2.50 mmol) and the resulting mixture was stirred at room temperature for 4.5 h. The standard workup and purification of the residue by column chromatography (25% EtOAc/hexane) gave the *enamide* **414** (80 mg, 56%) as a pale yellow oil. $R_f$ = 0.33 (30% EtOAc/hexane); IR (film) 2968, 1750 (C=O), 1637, 1454, 1408, 1227, 1123, 1039, 916, 757 $cm^{-1}$; $^1H$ NMR (360 MHz, $CDCl_3$) δ 7.32-7.25 (2H, m, Ar**H**), 7.22-7.13 (3H, m, Ar**H**), 5.79 (1H, ddt, *J* = 16.8, 10.1, 6.5 Hz, C**H**=$CH_2$), 5.12 (1H, ddt, *J* = 16.8, 3.3, 1.7 Hz, CH=C**H**$_2$), 5.06 (1H, ddt, 10.1, 3.3, 1.4 Hz, CH=C**H**$_2$), 4.23 (2H, app t, *J* = 8.0 Hz, C**H**$_2$O), 3.38-3.18 (2H, m, C**H**$_2$N), 3.03 (2H, d, *J* = 6.5 Hz C**H**$_2$CH=$CH_2$), 2.78-2.71 (2H, m, C**H**$_2$C**H**$_2$Ph), 2.42-2.34 (2H, m, C**H**$_2$C**H**$_2$Ph), 2.23 (2H, q, *J* = 7.6 Hz, C**H**$_2$$CH_3$), 1.11 (3H, t, *J* = 7.6 Hz, $CH_2$C**H**$_3$); $^{13}C$ NMR (90.6 MHz, $CDCl_3$) δ 156.8 (C), 142.1 (C), 141.3 (C), 134.9 (CH), 128.4 (2 x CH), 128.3 (2 x CH), 126.9 (C), 125.9 (CH), 116.8 ($CH_2$), 62.0 ($CH_2$), 46.1 ($CH_2$), 34.0 ($CH_2$), 33.9 ($CH_2$), 33.2 ($CH_2$), 23.9 ($CH_2$), 13.1 ($CH_3$); HRMS (ES) Exact mass calcd for $C_{18}H_{24}NO_2$ $[M+H]^+$: 286.1802, found: 286.1798.




**3-[(*Z*)-4-(*tert*-Butyldimethylsilyloxy)-2-ethyl-1-thiophen-2-ylbut-1-enyl]oxazolidin-2-one (416b)**. General Procedure I was followed using ynamide **394e** (135 mg, 0.50 mmol) to produce

the corresponding alkenylzinc species. To this solution was added a solution of $Pd_2dba_3$ (11 mg, 0.0125 mmol), tri(2-furyl)phosphine (11.0 mg, 0.05 mmol) and 2-iodothiophene (168 mg, 0.80 mmol) in THF (3 mL + 2 mL rinse) *via* cannula and the resulting mixture was heated at 65 °C for 40 h. The standard workup and purification of the residue by column chromatography (10% EtOAc/hexane→50% EtOAc/hexane) gave the *enamide* **416b** (85 mg, 45%) as a yellow-brown oil. $R_f$ = 0.47 (30% EtOAc/hexane); IR (film) 2929, 2360, 1751 (C=O), 1469, 1410, 1415, 1410, 1263, 1092, 908, 835, 735 $cm^{-1}$; $^1H$ NMR (360 MHz, $CDCl_3$) δ 7.30 (1H, dd, *J* = 4.9, 1.5 Hz, Ar**H**), 7.02-6.98 (2H, m, Ar**H**), 4.39-4.31 (2H, m, OC**H**$_2$CH$_2$N), 3.80 (2H, t, *J* = 7.0 Hz, C**H**$_2$OSi), 3.60 (2H, app dd, *J* = 8.7, 7.3 Hz, C**H**$_2$N), 2.52 (1H, t, *J* = 7.0 Hz, C**H**$_2$CH$_2$OSi), 2.29 (2H, q, *J* = 7.5 Hz, C**H**$_2$CH$_3$), 1.07 (3H, t, *J* = 7.5 Hz, CH$_2$C**H**$_3$), 0.91 (9H, s, C(C**H**$_3$)$_3$), 0.08 (6H, s, Si(C**H**$_3$)$_2$); $^{13}C$ NMR (62.9 MHz, $CDCl_3$) δ 156.7 (C), 144.8 (C), 137.7 (C), 127.5 (CH), 126.8 (CH), 125.8 (CH), 123.7 (C), 62.0 ($CH_2$), 61.2 ($CH_2$), 45.7 ($CH_2$), 34.4 ($CH_2$), 25.9 (3 x $CH_3$), 25.3 ($CH_2$), 18.3 (C), 13.1 ($CH_3$), –5.3 (2 x $CH_3$); HRMS (ES) Exact mass calcd for $C_{19}H_{32}NO_3SSi$ $[M+H]^+$: 382.1867, found: 382.1863.

**3-[(*E*)-2-(4-Nitrophenyl)-2-(2-oxooxazolidin-3-yl)-1-phenylvinyl]benzoic acid ethyl ester (418) and 3-(*E*)-2-(2-oxooxazolidin-3-yl)-1-phenylvinylbenzoic acid ethyl ester (396b)**

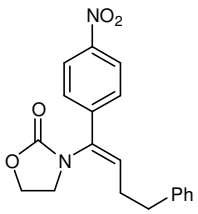



To a solution of ynamide **394b** (94 mg, 0.50 mmol) and Rh(cod)(acac) (7.8 mg, 0.025 mmol) in THF (5 mL) at 0 °C was added 3-(ethoxycarbonyl)phenylzinc iodide (0.5 M in THF, 1.10 mL, 0.55 mmol) over 1 min, and the reaction was then stirred at

room temperature for 15 min to produce the alkenylzinc species **417**. To this solution was added a solution of $Pd_2dba_3$ (11 mg, 0.0125 mmol), tri(2-furyl)phosphine (11 mg, 0.05 mmol) and 1-iodo-4-nitrobenzene (199 mg, 0.80 mmol) in THF (3 mL + 2 mL rinse) *via* cannula and the resulting mixture was heated at 65 °C for 48 h. The standard workup and purification of the residue by column chromatography (40% EtOAc/hexane) gave the *enamide* **396b** (34 mg, 20%) as a brown oil followed by the *enamide* **418** (42 mg, 18%) as an orange solid.

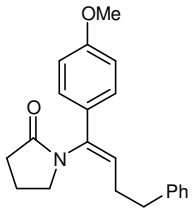
Data for **396b**: See page 165.

Data for **418**: $R_f$ = 0.28 (40% EtOAc/hexane); m.p. 146-148 °C; IR ($CHCl_3$) 3055, 2986, 1758 (C=O), 1716 (C=O), 1595, 1520, 1347, 1265, 896, 740 $cm^{-1}$; $^1H$ NMR (360 MHz, $CDCl_3$) δ 8.04 (2H, d, *J* = 8.9 Hz, Ar**H**), 7.89 (1H, dt, *J* = 7.5, 1.6 Hz, Ar**H**), 7.69 (1H, t, *J* = 1.6 Hz, Ar**H**), 7.42-7.32 (5H, m, Ar**H**), 7.30-7.16 (4H, m, Ar**H**), 4.33-4.23 (4H, m, OC**H**$_2$CH$_2$N and OC**H**$_2$CH$_3$), 3.52 (2H, app dd, *J* = 8.6, 7.3 Hz, C**H**$_2$N), 1.31 (3H, t, *J* = 7.1 Hz, OCH$_2$C**H**$_3$); $^{13}C$ NMR (90.6 MHz, $CDCl_3$) δ 165.9 (C), 155.8 (C), 147.0 (C), 143.3 (C), 142.1 (C), 140.1 (C), 140.0 (C), 135.2 (CH), 131.9 (CH), 131.4 (C), 130.7 (C), 130.4 (2 x CH), 129.1 (CH), 129.0 (2 x CH), 128.9 (2 x CH), 128.9 (CH), 128.5 (CH), 123.6 (2 x CH), 62.5 ($CH_2$), 61.1 ($CH_2$), 45.8 ($CH_2$), 14.2 ($CH_3$); HRMS (ES) Exact mass calcd for $C_{26}H_{26}N_3O_6$ $[M+NH_4]^+$: 476.1816, found: 476.1818.




**3-[(*Z*)-1-(4-Nitrophenyl)-2-phenylbut-1-enyl]oxazolidin-2-one (420a)**. General Procedure J was followed using ynamide **394a** (43 mg, 0.20 mmol) to produce the corresponding alkenylzinc species. To this solution was added a solution of $Pd_2dba_3$ (11 mg, 0.0125 mmol), tri(2-furyl)phosphine (11 mg, 0.05 mmol), and 1-iodo-4-nitrobenzene (199 mg, 0.80 mmol) in THF (3 mL + 2 mL rinse) *via* cannula and the resulting mixture was heated at 65 °C for 45 h. The standard workup and purification of the residue by column chromatography (2% EtOAc/hexane→20% EtOAc/hexane) gave the *enamide* **420a** (24 mg, 36%) as a brown solid. $R_f$ = 0.19 (30% EtOAc/hexane); m.p. decomposition observed before melting. IR ($CHCl_3$) 1755 (C=O), 1599, 1520 ($NO_2$), 1415, 1346, 1265, 1041, 908, 735, 650 $cm^{-1}$; $^1H$ NMR (360 MHz, $CDCl_3$) δ 8.21 (2H, d, *J* = 9.0 Hz, Ar**H**), 7.46 (2H, d, *J* = 9.0 Hz, Ar**H**),

7.34-7.30 (2H, m, Ar**H**), 7.24-7.19 (3H, m, Ar**H**), 6.22 (1H, t, *J* = 7.5 Hz, =C**H**), 4.45-4.41 (2H, m, C**H**$_2$O), 3.34-3.30 (2H, m, C**H**$_2$N), 2.88 (2H, t, *J* = 7.3 Hz, C**H**$_2$Ph), 2.60 (2H, app q, *J* = 7.3 Hz, C**H**$_2$CH$_2$Ph); $^{13}$C NMR (62.9 MHz, $CDCl_3$) δ 156.3 (C), 147.5 (C), 142.2 (C), 141.1 (C), 133.6 (CH), 133.1 (C), 128.5 (2 x CH), 128.5 (2 x CH), 126.5 (2 x CH), 126.3 (CH), 124.1 (2 x CH), 62.3 ($CH_2$), 45.3 ($CH_2$), 34.7 ($CH_2$), 30.6 ($CH_2$); HRMS (ES) Exact mass calcd for $C_{19}H_{22}N_3O_4$ $[M+NH_4]^+$: 356.1605, found: 356.1602.



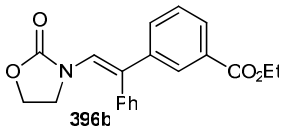

**1-[(*Z*)-1-(4-Methoxyphenyl)-4-phenylbut-1-enyl]pyrrolidin-2-one (420b)**. General Procedure J was followed using ynamide **394g** (43 mg, 0.20 mmol) to produce the corresponding alkenylzinc species. To this solution was added a solution of $Pd_2dba_3$ (11 mg, 0.0125 mmol), tri(2-furyl)phosphine (11 mg, 0.05 mmol), and 4-iodoanisole (187 mg, 0.80 mmol) in THF (3 mL + 2 mL rinse) *via* cannula and the resulting mixture was heated at 65 °C for 45 h. The standard workup and purification of the residue by column chromatography (10% EtOAc/hexane→40% EtOAc/hexane) gave the hydrometallation product **402f** (44 mg, 41%) as a yellow oil, followed by the *enamide* **420b** (25 mg, 18%) as a brown oil.

Data for **402f**: See page 175.

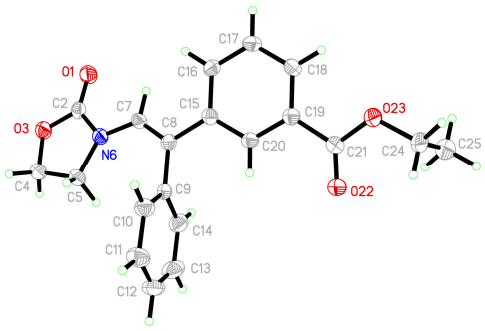
Data for **420b**: $R_f$ = 0.21 (50% EtOAc/hexane); IR (film) 2927, 1683 (C=O), 1608, 1511, 1461, 1418, 1250, 1175, 908, 733 cm$^{-1}$; $^1$H NMR (360 MHz, $CDCl_3$) δ 7.40-7.36 (2H, m, Ar**H**), 7.32-7.27 (5H, m, Ar**H**), 6.94 (2H, d, *J* = 8.9 Hz, Ar**H**), 6.01 (1H, t, *J* = 7.3 Hz, =C**H**), 3.89 (3H, s, OC**H**$_3$), 3.27 (2H, t, *J* = 7.0 Hz, C**H**$_2$N), 2.90 (2H, t, *J* = 7.5 Hz, C**H**$_2$C=O), 2.64 (3H, t, *J* = 8.1 Hz, C**H**$_2$Ph), 2.52 (2H, app q, *J* = 7.4 Hz, C**H**$_2$CH$_2$Ph), 2.16 (2H, app quintet, *J* = 7.5 Hz, C**H**$_2$CH$_2$N); $^{13}$C NMR (90.6 MHz, $CDCl_3$) δ 174.1 (C), 159.5 (C), 141.7 (C), 135.0 (C), 128.6 (C), 128.5 (2 x CH), 128.3 (2 x CH), 127.0 (2 x CH), 126.2 (CH), 125.9 (CH), 113.9 (2 x CH), 55.3 ($CH_3$), 48.4 ($CH_2$), 35.1 ($CH_2$), 31.1 ($CH_2$), 30.4 ($CH_2$), 18.9 ($CH_2$); HRMS (ES) Exact mass calcd for $C_{21}H_{24}NO_2$ $[M+H]^+$: 322.1802, found: 322.1804.

### 6.2.6 Regio-/Stereochemical Determinations

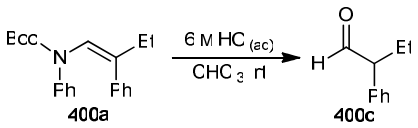
- The regioselectivities of the rhodium-catalysed carbozincation reactions of alkyl-substituted ynamides **396a, 396c, 396d, 396f** and **396g** using organozinc halide reagents were obvious from the $^1$H NMR spectra of the corresponding enamide products (by consideration of the signals of the alkene proton, which did not exhibit vicinal proton–proton coupling).
- The regio- and stereoselectivity of carbometallation of ynamide **394b** with arylzinc halide **397a** was established through X-ray crystallography of the resulting enamide **396b**:



396b




- The regio-/stereoselectivities of the remaining carbozincation reactions using organozinc halide reagents were assigned by analogy.
- The regiochemical outcome of the copper-catalysed carbozincation of ynamide **395b** to produce enamide **400a** was determined through hydrolysis of **400a** according to the following procedure:

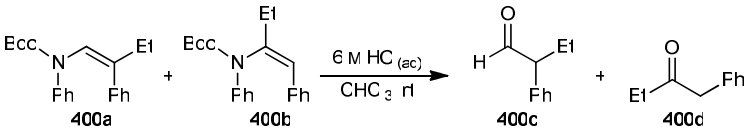


400a 400c

A solution of the enamide **400a** (32 mg, 0.10 mmol) in aqueous HCl (6 M, 1 mL, 6 mmol) and $CHCl_3$ (2 mL) was stirred at room temperature for 4 h. The reaction was quenched carefully with saturated $NaHCO_3$ solution (5 mL) and

extracted with $CHCl_3$ (3 x 5 mL). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo* to afford a pale yellow oil. $^1H$ NMR analysis of the unpurified reaction mixture revealed that enamide **400a** had been partially converted into the known aldehyde, phenylbutyraldehyde (**400c**).[185]

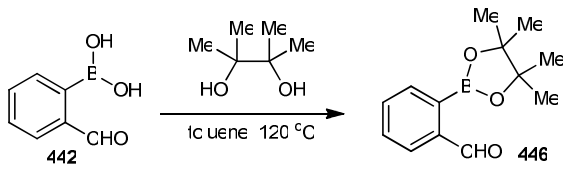
- The regiochemical outcome of the rhodium-catalysed carbozincation of ynamide **395b** to produce enamides **400a** and **400b** was determined through hydrolysis of the mixture according to the following procedure:



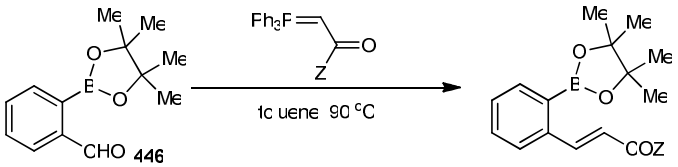

A solution of the mixture of **400a** and **400b** (16 mg, 0.05 mmol) in HCl (6 M, 0.50 mL, 3.0 mmol) and $CHCl_3$ (1.0 mL) was stirred at room temperature for 4 h. The reaction was quenched carefully with saturated $NaHCO_3$ solution (5 mL) and extracted with $CHCl_3$ (3 x 5 mL). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo* to afford a pale yellow oil. $^1H$ NMR analysis of the unpurified reaction mixture revealed that presence of the known aldehyde, 2-phenylbutyraldehyde (**400c**),[185] and the commercially available ketone, 1-phenyl-2-butanone (**400d**), confirming that the enamide mixture contained regioisomers rather than *E*/*Z* stereoisomers of **400a**.

## 6.3 Rhodium-Catalysed Carbometallation–Conjugate Addition Reaction

### 6.3.1 Preparation of Boronate Ester Coupling Partners



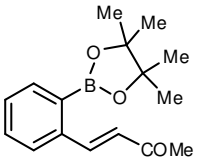

**2-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)benzaldehyde (446)**.[174a] Pinacol (2.17 g, 18.4 mmol) was added to a suspension of 2-formylphenylboronic acid (2.50 g, 16.7 mmol) in toluene (30 mL) and a Dean-Stark trap was attached. The mixture was refluxed for 19 h and then filtered through a plug of $MgSO_4$. The filtrate was concentrated *in vacuo* to afford the title compound as a yellow oil (3.94 g, 16.9 mmol, >99%) that displayed identical spectroscopic data to those reported previously.[174a] The compound was used in subsequent steps without further purification. $R_f$ = 0.63 (30% EtOAc/hexane); IR (film) 2980, 1697 (C=O), 1347, 1258, 1203, 1114, 1069, 910, 858, 734 $cm^{-1}$; $^1H$ NMR (360 MHz, $CDCl_3$) δ 10.58 (1H, s, C**H**O), 8.01-7.98 (1H, m, Ar**H**), 7.91-7.89 (1H, m, Ar**H**), 7.65-7.57 (2H, m, Ar**H**), 1.43 (12H, s, 4 x C**H**$_3$); $^{13}C$ NMR (90.6 MHz, $CDCl_3$) δ 194.6 (CH), 141.2 (C), 135.4 (CH), 132.9 (CH), 130.7 (CH), 127.9 (CH), 84.4 (2 x C), 24.8 (4 x $CH_3$). A signal for the C attached to B is not observed due to complex splitting.



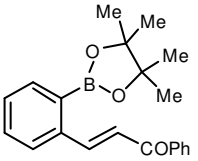

**General Procedure K**

The ylide (1.3 equiv) was added to a stirred solution of 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzaldehyde **446** (1 equiv) in toluene (2 mL/mmol of boronate

ester). The reaction mixture was heated to 90 °C until TLC analysis indicated complete consumption of starting material, then cooled to room temperature and concentrated *in vacuo*. The residue was suspended in ether, filtered to remove triphenylphosphine oxide and the filtrate was then concentrated *in vacuo*. Purification by silica column chromatography gave the desired product.

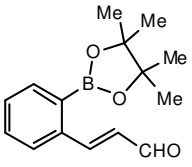



**(*E*)-4-[2-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]but-3-en-2-one (444)**.[174a] The title compound was prepared according to General Procedure K using triphenylphosphoranylidene-2-propanone (2.67 g, 8.40 mmol) and 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzaldehyde **446** (1.50 g, 6.46 mmol) for a reaction time of 18 h. Purification by silica column chromatography (30% EtOAc/hexane) gave the title compound as a white solid (1.50 g, 85%, >19:1 *E/Z*) that displayed identical spectroscopic data to those reported previously.[174a] $R_f$ = 0.60 (30% EtOAc/hexane); IR ($CHCl_3$) 2981, 1652 (C=O), 1558, 1507, 1348, 1264, 1144, 908, 738, 651 $cm^{-1}$; $^1H$ NMR (360 MHz, $CDCl_3$) δ 8.45 (1H, d, *J* = 16.5 Hz, C**H**=CHCOCH$_3$), 7.82 (1H, dd, *J* = 7.9, 1.2 Hz, Ar**H**), 7.62 (1H, dd, *J* = 7.9, 1.2 Hz, Ar**H**), 7.40 (1H, td, *J* = 7.9, 1.2 Hz, Ar**H**), 7.31 (1H, td, *J* = 7.9, 1.2 Hz, Ar**H**), 6.51 (1H, d, *J* = 16.5 Hz, CH=C**H**COCH$_3$), 2.35 (3H, s, COC**H**$_3$), 1.31 (12H, s, 2 x C(C**H**$_3$)$_2$); $^{13}C$ NMR (90.6 MHz, $CDCl_3$) δ 199.6 (C), 145.6 (CH), 140.5 (C), 136.5 (CH), 131.3 (CH), 129.2 (CH), 128.7 (CH), 125.6 (CH), 84.1 (2 x C), 26.2 ($CH_3$), 24.9 (4 x $CH_3$). A signal for the C attached to B is not observed due to complex splitting.

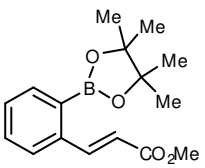



**(*E*)-1-Phenyl-3-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenylpropenone (447a)**. The title compound was prepared according to General Procedure K using 1-phenyl-2-triphenylphosphanylidene ethanone (745 mg, 1.96 mmol) and 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzaldehyde **446** (350 mg, 1.50 mmol) for a reaction time of 16 h. Purification by silica column chromatography (30% EtOAc/hexane) gave the title compound as an orange solid (312 mg, 62%). $R_f$ = 0.69 (30% EtOAc/hexane); m.p. 88-90 °C; IR ($CHCl_3$) 2981, 1606 (C=O), 1481, 1445, 1350, 1144, 909, 860,

735, 650 $cm^{-1}$; $^1H$ NMR (360 MHz, $CDCl_3$) δ 8.51 (1H, d, *J* = 16.0 Hz, C**H**=CHCOPh), 7.90 (2H, d, *J* = 7.4 Hz, Ar**H**), 7.79 (1H, d, *J* = 7.4 Hz, Ar**H**), 7.74 (1H, d, *J* = 7.9 Hz, Ar**H**), 7.49 (1H, t, *J* = 7.4 Hz, Ar**H**), 7.41 (3H, app t, *J* = 7.7 Hz, Ar**H**), 7.31 (1H, t, *J* = 7.4 Hz, Ar**H**), 7.25 (1H, d, *J* = 16.0 Hz, CH=C**H**COPh ), 1.25 (12H, s, 2 x C(C**H**$_3$)$_2$); $^{13}C$ NMR (90.6 MHz, $CDCl_3$) δ 192.5 (C), 146.5 (CH), 140.7 (C), 138.4 (C), 136.3 (CH), 132.2 (CH), 131.1 (CH), 129.2 (CH), 128.7 (2 x CH), 128.4 (2 x CH), 125.6 (CH), 124.4 (CH), 84.1 (2 x C), 24.8 (4 x $CH_3$). A signal for the C attached to B is not observed due to complex splitting.; HRMS (ES) Exact mass calcd for $C_{21}H_{24}BO_3$ $[M+H]^+$: 335.1813, found: 335.1814.

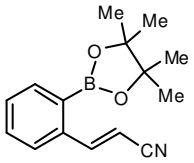



**(*E*)-3-[2-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]propenal (447b)**.[174a] The title compound was prepared according to slightly modified General Procedure K using (triphenylphosphoranylidene)acetaldehyde (1.98 g, 6.5 mmol) and 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzaldehyde **446** (1.16 g, 5.0 mmol). The reaction mixture was stirred at rt overnight and then heated to 50 $^oC$ for 4 h, then cooled to room temperature and concentrated *in vacuo*. Purification by silica column chromatography (20% EtOAc/hexane) gave the title compound as a pale yellow solid (894 mg, 69%) that displayed identical spectroscopic data to those reported previously.[174a] $R_f$ = 0.53 (20% EtOAc/hexane); IR ($CHCl_3$) 2981, 1675 (C=O), 1445, 1380, 1347, 1274, 1144, 909, 732, 650 $cm^{-1}$; $^1H$ NMR (360 MHz, $CDCl_3$) δ 9.74 (1H, d, *J* = 7.8 Hz, C**H**O), 8.49 (1H, d, *J* = 15.9 Hz, C**H**=CHCHO), 7.93 (1H, d, *J* = 7.4 Hz, Ar**H**), 7.73 (1H, d, *J* = 7.4 Hz, Ar**H**), 7.50 (1H, t, *J* = 7.4 Hz, Ar**H**), 7.43 (1H, t, *J* = 7.4 Hz, Ar**H**), 6.68 (1H, dd, *J* = 15.9, 7.8 Hz, CH=C**H**CHO), 1.39 (12H, s, 2 x C(C**H**$_3$)$_2$); $^{13}C$ NMR (90.6 MHz, $CDCl_3$) δ 194.5 (CH), 154.1 (CH), 139.8 (C), 136.7 (CH), 131.3 (CH), 129.9 (CH), 129.4 (CH), 126.1 (CH), 84.2 (2 x C), 24.9 (4 x $CH_3$). A signal for the C attached to B is not observed due to complex splitting.



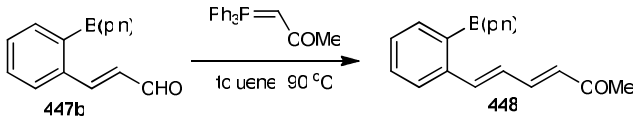

**Methyl (2*E*)-3-[2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]acrylate (447c)**.[174a] The title compound was prepared according to General Procedure K using methyl

(triphenylphosphoranylidene) acetate (2.81 g, 8.40 mmol) and 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzaldehyde **446** (1.50 g, 6.46 mmol) for a reaction time of 20 h. Purification by silica column chromatography (30% EtOAc/hexane) gave the title compound as a pale yellow solid (1.52 g, 82%) as a mixture of the *E*- and *Z*-isomers (10:1) that displayed identical spectroscopic data to those reported previously.[174a] $R_f$ = 0.63 (30% EtOAc/hexane); IR ($CHCl_3$) 2982, 1716 (C=O), 1635, 1350, 1320, 1265, 1145, 909, 741, 651 $cm^{-1}$; $^1H$ NMR (360 MHz, $CDCl_3$) δ 8.58 (1H, d, *J* = 16.0 Hz, C**H**=CHCO$_2$CH$_3$), 7.84 (1H, dd, *J* = 7.3, 1.2 Hz, Ar**H**), 7.68 (1H, app d, *J* = 8.0 Hz, Ar**H**), 7.45 (1H, td, *J* = 7.6, 1.2 Hz, Ar**H**), 7.37 (1H, td, *J* = 7.6, 1.2 Hz, Ar**H**), 6.39 (1H, d, *J* = 16.0 Hz, CH=C**H**CO$_2$CH$_3$), 3.82 (3H, s, CO$_2$C**H**$_3$), 1.39 (12H, s, 2 x C(C**H**$_3$)$_2$); $^{13}C$ NMR (90.6 MHz, $CDCl_3$) δ 167.6 (C), 145.9 (CH), 140.1 (C), 136.1 (CH), 131.0 (CH), 129.0 (CH), 125.6 (CH), 118.5 (CH), 84.1 (2 x C), 51.5 ($CH_3$), 24.8 (4 x $CH_3$). A signal for the C attached to B is not observed due to complex splitting.



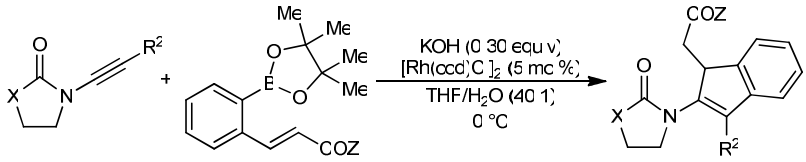

**(*E*)-3-[2-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]acrylonitrile (447d)**.[174a] (Triphenylphosphanylidene) acetonitrile (1.04 g, 3.45 mmol) was added to a stirred solution of 2-(4,4,5,5,-tetramethyl-1,3,2-dioxaborolan-2-yl)benzaldehyde **446** (615 mg, 2.65 mmol) in toluene (10 mL). The reaction mixture was heated to 90 $^oC$ for 20 h, then cooled to room temperature and concentrated *in vacuo*. Purification by silica column chromatography (15→30% EtOAc/hexane) gave the title compound as a pale yellow solid (620 mg, 92%) as a mixture of the *E*- and *Z*-isomers (6:1). that displayed identical spectroscopic data to those reported previously.[174a] $R_f$ = 0.62 (30% EtOAc/hexane); IR ($CHCl_3$) 2982, 2929, 2219 (C≡N), 1381, 1348, 1273, 1144, 908, 739, 651 $cm^{-1}$; $^1H$ NMR (360 MHz, $CDCl_3$) δ 8.38 (1H, d, *J* = 16.7 Hz, C**H**=CHCN), 7.91 (1H, d, *J* = 7.3 Hz, Ar**H**), 7.59 (1H, d, *J* = 7.9 Hz, Ar**H**), 7.52-7.37 (2H, m, Ar**H**), 5.84 (1H, d, *J* = 16.7 Hz, CH=C**H**CN), 1.38 (12H, s, 2 x C(C**H**$_3$)$_2$); $^{13}C$ NMR (62.9 MHz, $CDCl_3$) δ 1151.7 (CH), 139.3 (C), 136.7 (CH), 131.3 (CH), 129.8 (CH), 124.7 (CH), 118.7 (C), 96.8 (CH), 84.2 (2 x C), 24.8 (4 x $CH_3$). A signal for the C attached to B is not observed due to complex splitting.

**(3*E*,5*E*)-6-[2-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]hexa-3,5-dien-2-one (448)**



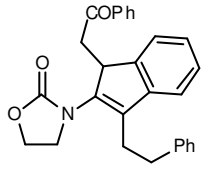

Triphenylphosphoranylidene-2-propanone (207 mg, 0.65 mmol) was added to a stirred solution of (*E*)-3-[2-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]propenal **447b** (129 mg, 0.50 mmol) in toluene (0.50 mL). The reaction mixture was heated to 90 °C for 16 h, then cooled to room temperature and concentrated *in vacuo*. The residue was was purified by silica column chromatography (20% EtOAc/hexane) to give the title compound as a yellow solid (122 mg, 82%, >19:1 *E/Z*). $R_f$ = 0.47 (30% EtOAc/hexane); m.p. 105-106 °C; IR ($CHCl_3$) 2979, 1662 (C=O), 1590, 1481, 1346, 1252, 1145, 999, 862, 658 $cm^{-1}$; $^1H$ NMR (360 MHz, $CDCl_3$) δ 7.92-7.81 (2H, m, Ar**H** and C**H**=CHCH=CHCOCH$_3$), 7.70 (1H, d, *J* = 8.0 Hz, Ar**H**), 7.44 (1H, t, *J* = 7.6 Hz, Ar**H**), 7.36 (1H, dd, *J* = 15.4, 10.9, CH=C**H**CH=CHCOCH$_3$), 7.31 (1H, td, *J* = 7.4, 1.1 Hz, Ar**H**), 6.86 (1H, ddd, *J* = 15.5, 10.9, 0.6 Hz, CH=CHC**H**=CHCOCH$_3$), 6.28 (1H, d, *J* = 15.5 Hz, CH=C**H**COCH$_3$), 2.34 (3H, s, COC**H**$_3$), 1.38 (12H, s, 2 x C(C**H**$_3$)$_2$); $^{13}C$ NMR (90.6 MHz, $CDCl_3$) δ 198.5 (C), 144.1 (CH), 142.4 (CH), 141.8 (C), 136.5 (CH), 131.1 (CH), 129.9 (CH), 128.1 (CH), 127.4 (CH), 125.0 (CH), 83.9 (2 x C), 27.7 ($CH_3$), 24.9 (4 x $CH_3$). A signal for the C attached to B is not observed due to complex splitting. HRMS (ES) Mass calculated for $C_{18}H_{24}O_3B$ $[M+H]^+$: 298.1849, found: 298.1849.

### 6.3.2 Rhodium-Catalysed Carbometallation–Conjugate Addition Reactions



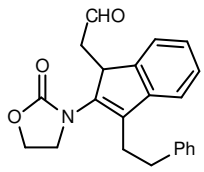

**General Procedure L**

The THF/$H_2O$ solvent (2 mL, 40:1) was added to a flask containing the ynamide (0.20 mmol), boronate ester (0.24 mmol), $[Rh(cod)Cl]_2$ (4.9 mg, 0.01 mmol) and KOH (3.4 mg, 0.06 mmol) at 0 $^oC$. The reaction mixture was stirred at 0 °C until the reaction had stopped progressing as observed by TLC analysis. The mixture was filtered through a short pad of silica gel gel using $CH_2Cl_2$ (10 mL) as eluent, and the filtrate was concentrated *in vacuo*. Purification of the residue by column chromatography afforded the desired enamide.

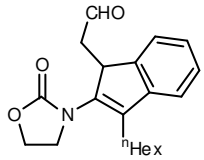


**3-[1-(2-Oxo-2-phenylethyl)-3-phenylindan-2-yl]oxazolidin-2-one (449a)**. The title compound was prepared according to General Procedure L using ynamide **394a** (43 mg, 0.20 mmol) and boronate **447a** (80 mg, 0.24 mmol) for a reaction time of 2.5 h. The residue was purified by column chromatography (90% $CH_2Cl_2$/hexane) to afford the title compound as a mixture of regioisomers (≥10:1) as a yellow oil (82 mg, 97%). $R_f$ = 0.33 (100% $CH_2Cl_2$); IR (film) 3027, 2922, 1750 (C=O), 1682 (C=O), 1420, 1469, 1224, 1044, 908, 736, 650 $cm^{-1}$; $^1H$ NMR (360 MHz, $CDCl_3$) δ 7.96-7.75 (2H, m, Ar**H**), 7.48 (1H, t, *J* = 7.4 Hz, Ar**H**), 7.41-7.32 (3H, m, Ar**H**), 7.27 (2H, m, Ar**H**), 7.21-7.02 (6H, m, Ar**H**), 4.27 (1H, app t, *J* = 6.6 Hz, C**H**$CH_2$C=O), 4.13-4.00 (2H, m, C**H**$_2$O), 3.65-3.58 (1H, m, C**H**$_2$N), 3.18 (1H, dd, *J* = 17.7, 6.6 Hz, C**H**$_2$C=O), 3.07 (1H, dd, *J* = 17.7, 6.6 Hz, C**H**$_2$C=O), 2.99-2.93 (1H, m, C**H**$_2$N), 2.85-2.72 (3H, m, C**H**$_2$C**H**$_2$Ph), 2.61 (1H, td, *J* = 8.7, 6.8 Hz, C**H**$_2$C**H**$_2$Ph); $^{13}C$ NMR (62.9 MHz, $CDCl_3$) δ 199.1 (C), 156.1 (C), 144.4 (C), 142.4 (C), 141.9 (C), 138.8 (C), 136.7 (C), 136.5 (C), 133.5 (CH), 128.7 (2 x CH), 128.7 (2 x CH), 128.2 (2 x CH), 128.1 (2 x CH), 127.1 (CH), 126.0 (CH), 125.8 (CH), 123.4 (CH), 119.8 (CH), 62.4 ($CH_2$), 46.5

($CH_2$), 42.8 (CH), 39.7 ($CH_2$), 33.8 ($CH_2$), 27.6 ($CH_2$); HRMS (ES) Mass calculated for $C_{28}H_{26}NO_3$ $[M+H]^+$: 424.1907, found: 424.1907.

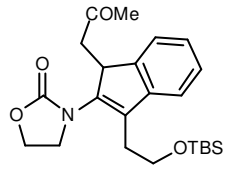



**[2-(2-Oxooxazolidin-3-yl)-3-phenethyl-1*H*-inden-1-yl]acetaldehyde (449b)**. The title compound was prepared according to General Procedure L using ynamide **394a** (43 mg, 0.20 mmol) and boronate **447b** (62 mg, 0.24 mmol) for a reaction time of 1.5 h. The residue was purified by column chromatography (100% $CH_2Cl_2$→5% acetone/$CH_2Cl_2$ then recolumned 40% EtOAc/hexane) to afford the title compound as a mixture of regioisomers (6.7:1) as a yellow oil (52 mg, 75%). $R_f$ = 0.19 (40% EtOAc/hexane); IR (film) 2920, 1748 (C=O), 1640, 1418, 1223, 1137, 1046, 907, 731, 650 $cm^{-1}$; $^1H$ NMR (360 MHz, $CDCl_3$) δ 9.63 (1H, s, C**H**O), 7.35-7.24 (3H, m, Ar**H**), 7.18 (3H, t, *J* = 6.2 Hz, Ar**H**), 7.10 (1H, t, *J* = 7.3 Hz, Ar**H**), 7.04 (2H, d, *J* = 7.3 Hz, Ar**H**), 4.25-4.09 (3H, m, C**H**$CH_2$C=O and C$\mathbf{H}_2$O), 3.61 (1H, dd, *J* = 16.6, 8.5 Hz, C$\mathbf{H}_2$N), 2.98-2.87 (1H, m, C$\mathbf{H}_2$N), 2.84-2.69 (5H, m, C$\mathbf{H}_2$C$\mathbf{H}_2$Ph and C$\mathbf{H}_2$C=O), 2.64 (1H, dd, *J* = 17.8, 6.0 Hz, C$\mathbf{H}_2$C=O); $^{13}C$ NMR (62.9 MHz, $CDCl_3$) δ 201.1 (CH), 156.3 (C), 143.4 (C), 142.4 (C), 141.5 (C), 138.5 (C), 136.3 (C), 128.6 (2 x CH), 128.3 (2 x CH), 127.3 (CH), 126.1 (CH), 125.9 (CH), 123.2 (CH), 119.8 (CH), 62.5 ($CH_2$), 46.5 ($CH_2$), 44.5 ($CH_2$), 41.5 (CH), 33.9 ($CH_2$), 27.5 ($CH_2$); HRMS (ES) Mass calculated for $C_{22}H_{22}NO_3$ $[M+H]^+$: 348.1594, found: 348.1600.

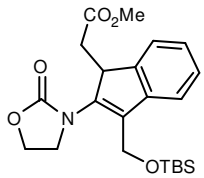



**[3-Hexyl-2-(2-oxooxazolidin-3-yl)-1*H*-inden-1-yl]acetaldehyde (449c)**. The title compound was prepared according to General Procedure L using ynamide **394c** (39 mg, 0.20 mmol) and boronate **447b** (62 mg, 0.24 mmol) for a reaction time of 1.5 h. The residue was purified by column chromatography (5% acetone/$CH_2Cl_2$ then 20% EtOAc/hexane) to afford the title compound as a yellow oil (44 mg, 67%). $R_f$ = 0.21 (40% EtOAc/hexane); IR (film) 2928, 1750 (C=O), 1638, 1416, 1264, 1095, 1045, 909, 736, 650 $cm^{-1}$; $^1H$ NMR (360 MHz, $CDCl_3$) δ 9.62 (1H, s, C**H**O), 7.31-7.12 (4H, m, Ar**H**), 4.41 (2H, t, *J* = 8.0 Hz, C$\mathbf{H}_2$O), 4.28 (1H, app t, *J* = 6.1 Hz, C**H**$CH_2$C=O), 4.11-4.00 (1H, m, C$\mathbf{H}_2$N), 3.64 (1H, app q, *J* = 8.0 Hz, C$\mathbf{H}_2$N), 2.80 (1H, dd, *J* = 17.4, 6.9 Hz,

CHC**H**$_2$C=O), 2.70 (1H, dd, *J* = 17.4, 5.7 Hz, CHC**H**$_2$C=O), 2.52-2.35 (2H, m, C**H**$_2$), 1.58-1.45 (2H, m, C**H**$_2$), 1.37-1.14 (6H, m, (C**H**$_2$)$_3$), 0.82 (3H, t, *J* = 6.7 Hz, C**H**$_3$); $^{13}$C NMR (62.9 MHz, $CDCl_3$) δ 201.4 (CH), 156.7 (C), 143.3 (C), 142.8 (C), 138.0 (C), 137.6 (C), 127.1 (CH), 125.8 (CH), 123.0 (CH), 119.9 (CH), 62.6 ($CH_2$), 47.3 ($CH_2$), 44.6 ($CH_2$), 41.8 (CH), 31.6 ($CH_2$), 29.6 ($CH_2$), 28.2 ($CH_2$), 25.4 ($CH_2$), 22.6 ($CH_2$), 14.0 ($CH_3$); HRMS (ES) Mass calculated for $C_{20}H_{26}NO_3$ $[M+H]^+$: 328.1926, found: 328.1907.

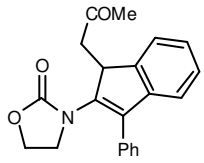



**3-[3-[2-(*tert*-Butyldimethylsilanyloxy)ethyl]-1-(2-oxopropyl)-1*H*-inden-2-yl]oxazolidin-2-one (449d)**. The title compound was prepared according to General Procedure L using ynamide **394e** (54 mg, 0.20 mmol) and boronate **444** (65 mg, 0.24 mmol) for a reaction time of 2.5 h. The residue was purified by column chromatography (0→5% acetone/$CH_2Cl_2$ then 30% EtOAc/hexane) to afford a yellow oil (79 mg, 95%). $R_f$ = 0.50 (50% EtOAc/hexane); IR (film) 3055, 2955, 1753 (C=O), 1717 (C=O), 1636, 1469, 1418, 1265, 1095, 740 cm$^{-1}$; $^1$H NMR (360 MHz, $CDCl_3$) δ 7.47-7.10 (4H, m, Ar**H**), 4.46 (2H, t, *J* = 8.0 Hz, C**H**$_2$O), 4.25 (1H, app t, *J* = 6.7 Hz, C**H**CH$_2$COCH$_3$), 4.11 (1H, app q, *J* = 8.3 Hz, C**H**$_2$OSi), 3.91-3.81 (2H, m, C**H**$_2$N), 3.73 (1H, app q, *J* = 7.9 Hz, C**H**$_2$OSi), 2.85-2.69 (4H, m, C**H**$_2$CH$_2$OSi and C**H**$_2$COCH$_3$), 2.17 (3H, s, COC**H**$_3$), 0.86 (9H, s, C(C**H**$_3$)$_3$), 0.00 (6H, s, Si(C**H**$_3$)$_2$); $^{13}$C NMR (90.6 MHz, $CDCl_3$) δ 207.9 (C), 156.8 (C), 143.9 (C), 142.6 (C), 139.9 (C), 135.5 (C), 127.0 (CH), 125.8 (CH), 122.9 (CH), 120.1 (CH), 62.6 ($CH_2$), 61.5 ($CH_2$), 47.4 ($CH_2$), 44.7 ($CH_2$), 42.8 ($CH_3$), 30.5 (CH), 29.1 ($CH_2$), 25.9 (3 x $CH_3$), 18.4 (C), -5.4 (2 x $CH_3$); HRMS (ES) Mass calculated for $C_{23}H_{37}N_2O_4Si$ $[M+NH_4]^+$: 433.2517, found: 433.2516.

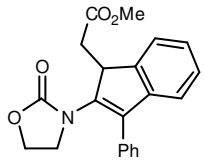



**3-(*tert*-Butyldimethylsilanyloxymethyl)-2-(2-oxooxazolidin-3-yl)-1*H*-inden-1-yl acetic acid methyl ester (449e)**. The title compound was prepared according to General Procedure L using ynamide **394d** (51 mg, 0.20 mmol) and boronate **447c** (69 mg, 0.24 mmol) for a reaction time of 1.5 h. The residue was purified by column chromatography (90→100% $CH_2Cl_2$/hexane→10% acetone/$CH_2Cl_2$) to afford the

title compound as a mixture of regioisomers (≥10:1) as a yellow solid (79 mg, 96%). $R_f$ = 0.24 (100% $CH_2Cl_2$); IR ($CHCl_3$) 2954, 2857, 1753 (C=O), 1469, 1418, 1264, 1095, 908, 734, 650 $cm^{-1}$; $^1H$ NMR (360 MHz, $CDCl_3$) δ 7.33 (1H, d, *J* = 7.4 Hz, Ar**H**), 7.26 (1H, d, *J* = 7.4 Hz, Ar**H**), 7.21 (1H, t, *J* = 7.4 Hz, Ar**H**), 7.11 (1H, t, *J* = 7.4 Hz, Ar**H**), 4.61 (1H, dd, *J* = 13.3, 1.2 Hz, C**H**$_2$OSi), 4.53 (1H, dd, *J* = 13.3, 1.2 Hz, C**H**$_2$OSi), 4.40-4.35 (2H, m, C**H**$_2$O), 4.21 (1H, t, *J* = 6.8 Hz, C**H**$CH_2CO_2CH_3$), 4.13 (1H, m, C**H**$_2$N), 3.73 (1H, dt, *J* = 15.8, 7.9 Hz, C**H**$_2$N), 3.60 (3H, s, OC**H**$_3$), 2.61-2.46 (2H, m, C**H**$_2CO_2CH_3$), 0.81 (9H, s, C(C**H**$_3)_3$), 0.00 (6H, d, *J* = 3.0 Hz, Si(C**H**$_3)_2$); $^{13}C$ NMR (90.6 MHz, $CDCl_3$) δ 172.6 (C), 156.2 (C), 142.9 (C), 141.8 (C), 139.3 (C), 134.2 (C), 127.1 (CH), 125.6 (CH), 122.9 (CH), 120.4 (CH), 62.6 ($CH_2$), 57.1 ($CH_2$), 51.8 ($CH_3$), 47.2 ($CH_2$), 44.0 (CH), 35.6 ($CH_2$), 25.9 (3 x $CH_3$), 18.3 (C), -5.3 ($CH_3$), -5.5 ($CH_3$); HRMS (ES) Mass calculated for $C_{22}H_{35}N_2O_5Si$ $[M+NH_4]^+$: 435.2310, found: 435.2312.

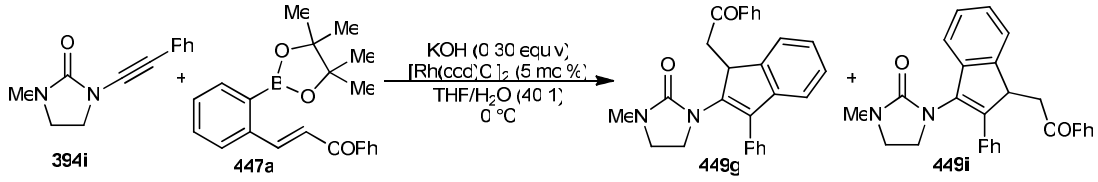



**3-[1-(2-Oxopropyl)-3-phenyl-1*H*-inden-2-yl]oxazolidin-2-one (445)**. The title compound was prepared according to General Procedure L using ynamide **394b** (37 mg, 0.20 mmol) and boronate **444** (65 mg, 0.24 mmol) for a reaction time of 2 h. The residue was purified by column chromatography (25% EtOAc/hexane) to afford the title compound as a yellow solid (47 mg, 71%). $R_f$ = 0.26 (30% EtOAc/hexane); m.p. 148-150 °C; IR ($CHCl_3$) 2955, 1749 (C=O), 1652, 1541, 1458, 1098, 1043, 908, 733, 650 $cm^{-1}$; $^1H$ NMR (360 MHz, $CDCl_3$) δ 7.52-7.35 (6H, m, Ar**H**), 7.26-7.22 (2H, m, Ar**H**), 7.19-7.14 (1H, m, Ar**H**), 4.76 (1H, dd, *J* = 6.9, 5.6 Hz, C**H**$CH_2COCH_3$), 4.33-4.25 (2H, m, C**H**$_2$O), 3.69-3.60 (1H, m, C**H**$_2$N), 3.39-3.32 (1H, m, C**H**$_2$N), 3.08 (1H, dd, *J* = 16.2, 5.6 Hz, CHC**H**$_2COCH_3$), 2.76 (1H, dd, *J* = 16.2, 6.9 Hz, CHC**H**$_2COCH_3$ ), 2.13 (3H, s, COC**H**$_3$); $^{13}C$ NMR (90.6 MHz, $CDCl_3$) δ 207.1 (C), 156.7 (C), 143.1 (C), 143.0 (C), 140.1 (C), 133.2 (C), 133.0 (C), 129.0 (2 x CH), 128.6 (2 x CH), 128.2 (CH), 127.0 (CH), 125.5 (CH), 123.1 (CH), 120.1 (CH), 62.8 ($CH_2$), 46.5 ($CH_2$), 44.6 ($CH_2$), 44.0 (CH), 30.6 ($CH_3$); HRMS (ES) Mass calculated for $C_{21}H_{23}N_2O_3$ $[M+NH_4]^+$: 351.1703, found: 351.1702.



**2-(2-Oxooxazolidin-3-yl)-3-phenyl-1*H*-inden-1-yl acetic acid methyl ester (449f)**. The title compound was prepared according to General Procedure L using ynamide **394b** (37 mg, 0.20 mmol) and boronate **447c** (69 mg, 0.24 mmol) for a reaction time of 2 h. The residue was purified by column chromatography (20% EtOAc/hexane) to afford the title compound as a yellow solid (52 mg, 75%). Slow diffusion of hexane into a solution of **449f** in EtOAc gave colourless crystals that were suitable for X-ray crystallography. $R_f$ = 0.29 (30% EtOAc/hexane); m.p. 117-119 °C; IR ($CHCl_3$) 2958, 1749 (C=O), 1699, 1458, 1407, 1264, 1043, 909, 734, 650 $cm^{-1}$; $^1H$ NMR (360 MHz, $CDCl_3$) δ 7.50-7.41 (6H, m, Ar**H**), 7.26-7.23 (2H, m, Ar**H**), 7.16-7.14 (1H, m, Ar**H**), 4.79 (1H, app t, *J* = 6.3 Hz, C**H**$CH_2CO_2CH_3$), 4.36-4.22 (2H, m, C**H**$_2$O), 3.64 (3H, s, OC**H**$_3$), 3.62-3.53 (1H, m, C**H**$_2$N), 3.37 (1H, m, C**H**$_2$N), 2.91 (1H, dd, *J* = 15.2, 6.3 Hz, CHC**H**$_2CO_2CH_3$), 2.74 (1H, dd, *J* = 15.2, 6.3 Hz, CHC**H**$_2CO_2CH_3$); $^{13}C$ NMR (90.6 MHz, $CDCl_3$) δ 171.9 (C), 156.5 (C), 143.0 (C), 142.5 (C), 139.9 (C), 133.4 (C), 132.0 (C), 129.1 (2 x CH), 128.7 (2 x CH), 128.2 (CH), 127.1 (CH), 125.5 (CH), 123.1 (CH), 119.9 (CH), 62.8 ($CH_2$), 51.7 ($CH_3$), 46.3 ($CH_2$), 44.6 (CH), 35.7 ($CH_2$); HRMS (ES) Mass calculated for $C_{21}H_{20}NO_4$ $[M+H]^+$: 350.1387, found: 350.1388.

**1-Methyl-3-[1-(2-oxo-2-phenylethyl)-3-phenyl-1*H*-inden-2-yl]imidazolidin-2-one (449g) and 1-Methyl-3-[3-(2-oxo-2-phenylethyl)-2-phenyl-3*H*-inden-1-yl]imidazolidin-2-one (449i)**

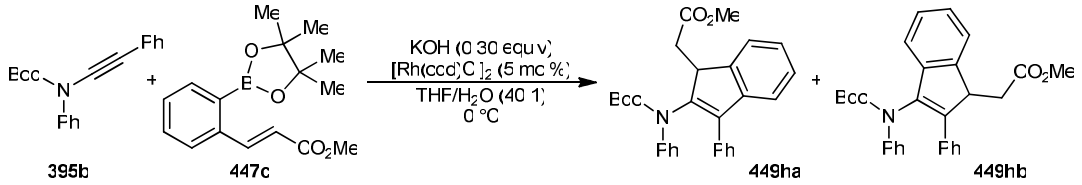



Ynamide **394i** (40 mg, 0.20 mmol) and boronate **447a** (80 mg, 0.24 mmol) underwent General Procedure L for a reaction time of 1.5 h. The residue was purified by column chromatography (40% EtOAc/hexane then 10% acetone/$CH_2Cl_2$) to afford the *enamide* **449g** (46 mg, 55%) as a yellow-orange solid followed by the *enamide* **449i** (23 mg, 28%) as an orange solid.

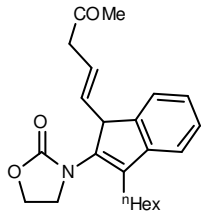
Data for **449g**: $R_f$ = 0.37 (50% EtOAc/hexane); m.p. 128-130 °C; IR ($CHCl_3$) 2900, 1696 (C=O), 1598, 1494, 1404, 1265, 1091, 908, 733, 650 $cm^{-1}$; $^1H$ NMR (360 MHz, $CDCl_3$) δ 8.01 (2H, dd, *J* = 8.4, 1.1 Hz, Ar**H**), 7.56 (1H, t, *J* = 7.4 Hz, Ar**H**), 7.50-7.33 (8H, m, Ar**H**), 7.18 (1H, t, *J* = 7.4 Hz, Ar**H**), 7.09 (2H, t, *J* = 7.4 Hz, Ar**H**), 5.19 (1H, dd, *J* = 8.8, 4.1 Hz, C**H**$CH_2$C=O), 3.58 (1H, dd, *J* = 16.3, 4.1 Hz, CHC**H**$_2$C=O), 3.46 (1H, ddd, *J* = 9.4, 9.2, 7.0 Hz, $CH_2$C**H**$_2$N), 3.28-3.05 (4H, m, C**H**$_2$C**H**$_2$N and CHC**H**$_2$C=O), 2.78 (3H, s, NC**H**$_3$); $^{13}C$ NMR (90.6 MHz, $CDCl_3$) δ 198.6 (C), 158.4 (C), 144.0 (C), 143.2 (C), 143.1 (C), 137.2 (C), 134.6 (C), 132.9 (CH), 129.5 (2 x CH), 128.5 (2 x CH), 128.3 (2 x CH), 128.2 (2 x CH), 127.7 (C), 127.5 (CH), 126.7 (CH), 124.4 (CH), 123.4 (CH), 119.1 (CH), 45.1 ($CH_2$), 44.7 (CH), 44.1 ($CH_2$), 40.5 ($CH_2$), 31.2 ($CH_3$); HRMS (ES) Exact mass calcd for $C_{27}H_{25}N_2O_2$ $[M+H]^+$: 409.1911, found: 409.1915.

Data for **449i**: $R_f$ = 0.23 (50% EtOAc/hexane); m.p. 64-66 °C; IR ($CHCl_3$) 2984, 1793, 1690 (C=O), 1445, 1265, 1226, 1094, 908, 735, 651 $cm^{-1}$; $^1H$ NMR (360 MHz, $CDCl_3$) δ 7.89 (2H, d, *J* = 7.4 Hz, Ar**H**), 7.54-7.51 (3H, m, Ar**H**), 7.44-7.36 (6H, m, Ar**H**), 7.29 (2H, t, J = 7.8 Hz, Ar**H**), 7.15 (1H, td, *J* = 7.4, 0.8 Hz, Ar**H**), 4.84 (1H, dd, *J* = 8.5, 4.5 Hz, C**H**$CH_2$C=O), 3.57-3.46 (2H, m, C**H**$_2$), 3.46-3.34 (2H, m, C**H**$_2$), 3.19-3.16 (2H, m, C**H**$_2$), 2.96 (3H, s, NC**H**$_3$); $^{13}C$ NMR (90.6 MHz, $CDCl_3$) δ 199.3 (C), 159.9 (C), 145.7 (C), 142.2 (C), 140.9 (C), 136.8 (C), 135.2 (C), 133.8 (C), 133.2 (CH), 128.7 (2 x CH), 128.6 (2 x CH), 128.5 (2 x CH), 128.2 (2 x CH), 127.8 (CH), 127.0 (CH), 125.8 (CH), 124.0 (CH), 120.1 (CH), 45.9 ($CH_2$), 43.8 (CH), 42.8 ($CH_2$), 40.6 ($CH_2$), 31.6 ($CH_3$); HRMS (ES) Exact mass calcd for $C_{27}H_{25}N_2O_2$ $[M+H]^+$: 409.1911, found: 409.1917.

**[2-(*tert*-Butoxycarbonylphenylamino)-3-phenyl-1*H*-inden-1-yl]acetic acid methyl ester (449ha) and [3-(*tert*-Butoxycarbonylphenylamino)-2-phenyl-1*H*-inden-1-yl]acetic acid methyl ester (449hb)**




Ynamide **395b** (59 mg, 0.20 mmol) and boronate **447c** (69 mg, 0.24 mmol) underwent General Procedure L for a reaction time of 2.5 h. Purification of the residue by column chromatography (100% $CH_2Cl_2$→5% acetone/$CH_2Cl_2$ then 1→2% EtOAc/petroleum ether) afforded a 2:1 inseparable mixture of *enamides* **449ha** and **449hb** (90 mg, 95%) as a pale yellow solid. $R_f$ = 0.38 (10% EtOAc/petroleum ether); m.p. 40-42 °C; IR ($CHCl_3$) 3054, 2984, 1709 (C=O), 1597, 1493, 1438, 1305, 1265, 1156, 739 $cm^{-1}$; $^1H$ NMR for major isomer **449ha** (360 MHz, $CDCl_3$) δ 7.57-7.00 (13H, m, Ar**H**), 6.83 (1H, d, *J* = 7.2 Hz, Ar**H**), 4.49 (1H, dd, *J* = 9.4, 4.0 Hz, C**H**$CH_2$), 3.64 (3H, s, OC**H**$_3$), 2.89 (1H, dd, *J* = 16.0, 4.0 Hz, CHC**H**$_2$), 2.38 (1H, dd, *J* = 16.0, 9.4 Hz, CHC**H**$_2$), 1.00 (9H, s, C(C**H**$_3$)$_3$); $^1H$ NMR for minor isomer **449hb** (360 MHz, $CDCl_3$) δ 7.57-7.00 (13H, m, Ar**H**), 6.94 (1H, t, *J* = 7.1 Hz, Ar**H**), 4.40 (1H, dd, *J* = 10.2, 4.1 Hz, C**H**$CH_2$), 3.64 (3H, s, OC**H**$_3$), 2.71 (1H, dd, *J* = 16.0, 4.1 Hz, CHC**H**$_2$), 2.20 (1H, dd, *J* = 16.0, 10.2 Hz, CHC**H**$_2$), 1.44 (9H, s, C(C**H**$_3$)$_3$); $^{13}C$ NMR (90.6 MHz, $CDCl_3$) Not fully assigned δ 172.9 (C), 172.6 (C), 153.7 (C), 152.4 (C), 144.6 (C), 142.0 (C), 141.2 (C), 140.8 (C), 138.3 (C), 135.6 (C), 134.1 (C), 133.1 (C), 129.1 (CH), 128.8 (CH), 128.7 (CH), 128.5 (CH), 128.4 (CH), 128.2 (CH), 127.9 (CH), 127.7 (CH), 127.3 (CH), 127.1 (CH), 125.8 (CH), 125.8 (CH), 125.6 (CH), 125.1 (CH), 124.7 (CH), 124.5 (CH), 123.7 (CH), 123.5 (CH), 123.4 (CH), 123.2 (CH), 119.9 (CH), 119.2 (CH), 81.3 (C), 81.1 (C), 51.8 (CH), 45.1 ($CH_3$), 44.6 ($CH_3$), 36.6 ($CH_2$), 36.2 ($CH_2$), 28.1 ($CH_3$), 27.5 ($CH_3$); HRMS (ES) Mass calculated for $C_{29}H_{30}NO_4$ $[M+H]^+$: 456.2169, found: 456.2173.

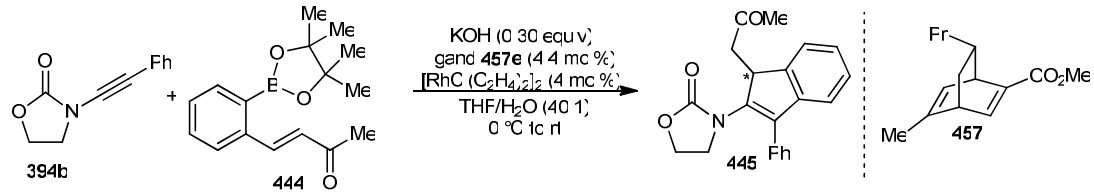


**3-[3-Hexyl-1-((*E*)-4-oxopent-2-enyl)-1*H*-inden-2-yl]oxazolidin-2-one (450)**. The title compound was prepared according to General Procedure L using ynamide **394c** (39 mg, 0.20 mmol) and boronate **448** (72 mg, 0.24 mmol) for a reaction time of 4 h. The residue was purified by column chromatography (10% acetone/$CH_2Cl_2$ then 20% EtOAc/hexane) to afford the title compound as an orange oil (34 mg, 47%). $R_f$ = 0.40 (50% EtOAc/hexane); IR (film) 2928, 1751 (C=O), 1714 (C=O), 1467, 1415, 1265, 1094, 907, 733, 651 $cm^{-1}$; $^1H$ NMR (360 MHz, $CDCl_3$) δ 7.31-7.22 (3H, m, Ar**H**), 7.21-7.13 (1H, m, Ar**H**), 5.99-5.88 (1H, m, CH=C**H**$CH_2COCH_3$), 5.16 (1H, dd, *J* = 15.3, 9.3 Hz, C**H**=$CHCH_2COCH_3$), 4.45 (2H, app t, *J* = 8.0 Hz, C**H**$_2$O), 4.40 (1H, d, *J* = 9.3 Hz, C**H**CH=CH), 4.04 (1H, app q, *J* = 8.3 Hz, C**H**$_2$N), 3.75 (1H, app q, *J* = 7.8 Hz, C**H**$_2$N), 3.21 (1H, dd, *J* = 16.9, 6.6 Hz, C**H**$_2COCH_3$), 3.12 (1H, dd, *J* = 16.9, 7.5 Hz, C**H**$_2$C=O), 2.56-2.45 (2H, m, C=CC**H**$_2(CH_2)_4$), 2.14 (3H, s, C**H**$_3$C=O), 1.66-1.52 (2H, m, C**H**$_2(CH_2)_3CH_3$), 1.40-1.19 (6H, m, (C**H**$_2)_3CH_3$), 0.86 (3H, t, *J* = 6.7 Hz, C**H**$_3$); $^{13}C$ NMR (90.6 MHz, $CDCl_3$) δ 206.5 (C), 156.5 (C), 143.2 (2 x C), 137.6 (C), 137.1 (C), 131.4 (CH), 127.3 (CH), 127.1 (CH), 125.5 (CH), 123.7 (CH), 119.6 (CH), 62.5 ($CH_2$), 52.0 ($CH_3$), 47.5 ($CH_2$), 47.1 ($CH_2$), 31.6 ($CH_2$), 29.6 ($CH_2$), 29.6 (CH), 28.0 ($CH_2$), 25.6 ($CH_2$), 22.6 ($CH_2$), 14.1 ($CH_3$); HRMS (ES) Mass calculated for $C_{23}H_{30}NO_3$ $[M+H]^+$: 368.2207, found: 368.2212.

### 6.3.3 Asymmetric Rhodium-Catalysed Carbometallation–Conjugate Addition Reactions

**Representative Procedure:**

**(-)3-[1-(2-Oxopropyl)-3-phenyl-1*H*-inden-2-yl]oxazolidin-2-one (445)** (Non-racemic)

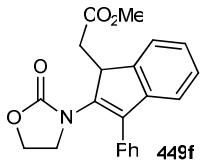



A solution of $[RhCl(C_2H_4)_2]_2$ (1.6 mg, 0.004 mmol) and ligand **457e** (1.0 mg, 0.0044 mmol) in THF (0.5 mL) was stirred at rt for 10 min then cooled to 0 °C. A solution

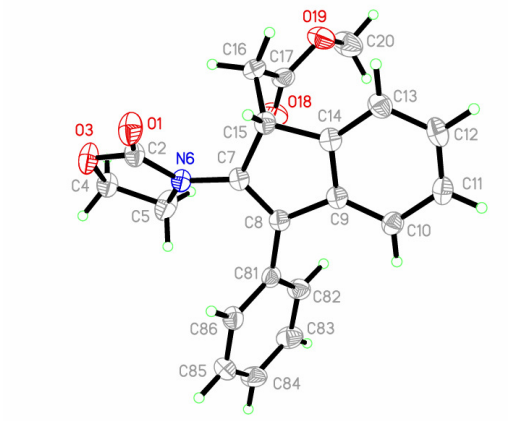
of the ynamide **394b** (19 mg, 0.10 mmol), boronate **444** (33 mg, 0.12 mmol) and KOH (1.7 mg, 0.03 mmol) in THF (0.50 mL) was then added, followed by $H_2O$ (24 μL). The reaction mixture was stirred at 0 °C for 1.5 h then warmed to rt. After 2 h, TLC analysis indicated complete consumption of starting material and the reaction mixture was filtered through a short pad of silica. Purification by column chromatography (25% EtOAc/hexane) gave a pure sample of the title compound suitable for HPLC analysis. For full data of **445** see page 191. Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (90:10 hexanes:isopropanol, 0.8 mL/min, 210 nm, 25 °C); $t_r$ (major) = 25.4 min, $t_r$ (minor) = 26.9 min; 67% ee; $[\alpha]_D^{24}$ –25.0 (c. 0.20, $CHCl_3$).

### 6.3.4 Regio-/Stereochemical Determinations

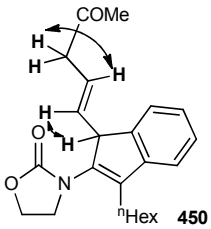
- The regio- and stereochemistry of enamide **449f** was established through X-ray crystallography.



449f




- The regio-/stereoselectivities of the remaining enamides resulting from the carbometallation–conjugate reactions (Table 5.1) were assigned by analogy.
- The regioselectivity and position of the pendant double bond of the enamide **450** was assigned after COSY analysis. The key correlations have been illustrated below.



450

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# Appendix

## List of Publications

1. **Diastereoselective Cobalt-Catalyzed Alkylative Aldol Cyclizations Using Trialkylaluminum Reagents.** Rudkin, M. E.; Joensuu, P. M.; MacLachlan, W. S.; Lam, H. W. *Org. Lett.* **2008**, *10*, 2939–2942.

2. **Preparation of Multisubstituted Enamides via Rhodium-Catalyzed Carbozincation and Hydrozincation of Ynamides.** Gourdet, B.; Rudkin, M. E.; Watts, C. A.; Lam, H. W. *J. Org. Chem.* **2009**, *74*, 7849–7858.